JOURNAL OF VIRAL HEPATITIS JVH

Journal of Viral Hepatitis, 2012, **19**, 560–567 doi:10.1111/j.1365-2893.2011.01576.x

HCV burden of infection in Egypt: results from a nationwide survey

J. Guerra,[1] M. Garenne, [1,2] M. K. Mohamed[3*] and A. Fontanet[1,4] [1]*Institut Pasteur, Unité d'épidémiologie des maladies émergentes, Paris, France;* [2]*Institut de Recherche pour le Développement, Paris, France;* [3]*Department of Community, Environmental and Occupational Medicine, Faculty of Medicine, Ain Shams University, Cairo, France; and* [4]*Conservatoire National des Arts et Métiers, Chaire Santé et Développement, Paris, France*

Received July 2011; accepted for publication November 2011

SUMMARY. Egypt is the country with the largest hepatitis C virus (HCV) epidemic in the world. In 2008, a Demographic Health Survey (DHS) was carried out in Egypt, providing for the first time a unique opportunity for HCV antibody testing on a nationwide representative sample of individuals. Consenting individuals answered a questionnaire on socio-demographic characteristics and iatrogenic exposures, before providing a blood sample for HCV antibody testing by enzyme-linked immunosorbent assay. Factors independently associated with HCV infection were examined through multivariate logistic regression models. Of 12 780 eligible subjects aged 15–59 years, 11 126 (87.1%) agreed to participate and provided a blood sample. HCV antibody prevalence nationwide was 14.7% (95% CI 13.9–15.5%) in this age group. HCV antibody prevalence gradually increased with age, reaching, in the 50–59 years age group, 46.3% and 30.8% in males and females, respectively. It was higher in males compared to females (17.4% versus 12.2%, respectively, $P < 0.001$), and in rural compared to urban areas (18.3% versus 10.3%, respectively, $P < 0.001$). In multivariate analysis, age, male sex, poverty, past history of intravenous anti-schistosomiasis treatment, blood transfusion, and living outside of the Frontier Governorates were all significantly associated with an increased risk of HCV infection. In addition, in urban areas, lack of education and being circumcised for females were associated with an increased risk of HCV infection. This study confirmed on a nationwide representative sample the very high HCV antibody prevalence in Egypt. It stresses the urgent need for strengthening prevention efforts, and bringing down the costs of antiviral drugs for countries like Egypt, where the people in the most precarious situations are also those most likely to be infected by the virus.

Keywords: Demographic and Health Survey, Egypt, epidemiology, hepatitis C virus, prevalence.

INTRODUCTION

Egypt has the highest hepatitis C virus (HCV) prevalence worldwide, with an estimated overall prevalence of 21.9% among adults in 1995–1996 [1]. This is markedly higher than in industrialised countries where the prevalence ranges from 0.5% to 2.3% [2]. It is also higher than in limited-resource countries, even those which reported high prevalence rates such as Pakistan (6.5%) and Mongolia (15.6%) [3].

The origin of the HCV epidemic in Egypt has been attributed to mass campaigns of parenteral anti-schistosomiasis treatment (PAT) in the 1960–1970s [1,4,5]. Treatment predominately targeted children and young adults living in schistosomiasis endemic areas, and consisted of weekly injections of antimony salts for 12–16 weeks. Insufficient sterilisation of the injecting equipment used during this mass treatment campaign is considered to be the cause of the HCV transmission at that time [1]. Despite the broadspread introduction of praziquantel in 1982, an oral drug to treat schistosomiasis [5], the transmission of HCV in Egypt has continued through a variety of mechanisms including blood transfusion [6–8], injections [4,6,9], dental treatment [6,7,9], surgery and invasive medical procedures [6,7,9–12], and instrumental delivery [6,7,9]. Most (>90%) HCV isolates found in Egypt belong to genotype 4 [13].

In 2008, following the recommendation of the National Committee for the Control of Viral Hepatitis [14], HCV antibody testing was incorporated into the Egypt Demographic and Health Survey (DHS) [15]. The DHS used a nationally representative sample of participants, and provided

Abbreviations: aOR, age-adjusted odds ratio; CIA, chemiluminescent microplate immunoassay; DHS, Demographic Health Survey; GEE, generalised estimated equations; HCV, hepatitis C virus.

Correspondence: Arnaud Fontanet, Unité d'épidémiologie des maladies émergentes, Institut Pasteur, 25, rue du Docteur Roux, Paris 75015, France. E-mail: fontanet@pasteur.fr
*Deceased.

a unique opportunity to obtain an estimate of HCV antibody prevalence nationwide. Results of the survey showed that HCV antibody prevalence remained high in Egypt, estimated at 14.7% for the 15–59 years old age group [15]. In this paper, we provide a more detailed analysis of these data and explore the factors associated with HCV infection in Egypt.

MATERIALS AND METHODS

Source of data

Data from DHS Surveys are freely available for academic research (http://www.measuredhs.com/).

Sampling strategy

To obtain a representative sample of the Egyptian population aged 15–59 years, a three-stage probability sample was designed, following a standard methodology developed for DHS surveys and adapted to the specific administrative units of the country surveyed [15]. As a result, 12 780 women and men aged 15–59 were asked to provide blood samples for hepatitis C testing, of whom 11 126 (87.1%) agreed. Informed consent for hepatitis C testing and interview was obtained from each respondent and from a parent or other guardian for minors. The blood samples were tested by a third generation enzyme-linked immunosorbent assay for detection of HCV antibody (Adaltis EIAgen HCV Ab, Adaltis Italia, Casalecchio di Reno, Italy) at the Central Laboratory (Cairo) and confirmed by a chemiluminescent microplate immunoassay (CIA) when positive. Sera positive for HCV antibodies were tested for HCV RNA at the Theodor Bilharz Institute in Cairo using the RealTime™ m2000 system (Abbott Laboratories, Abbott Park, IL, USA) [15].

Statistical analysis

HCV antibody prevalence rates and their 95% confidence intervals were estimated using sampling weights [16]. Factors associated with HCV infection were explored using logistic regression based on the information available in the DHS questionnaires: region of residence, type of residence (urban/rural), gender, marital status, educational attainment, knowledge about HCV, use of a water pipe to smoke tobacco, wealth index quintile of the household [17], health insurance coverage, number of people living in the household, and several iatrogenic factors (history of surgery, PAT, dental treatment, caesarean section, blood transfusion, injection, unsafe injection defined as a needle or syringe used to give an injection to someone else, and female circumcision). All associations were shown as age-adjusted odds ratio (aOR), with age introduced as a continuous variable in the model. Test of interactions were used to detect whether effects varied according to age (less and above 30 years), to sex, or to urban/rural residence. Since the effect of several variables differed significantly according to urban/rural residence, two separate models were built, one for urban areas, and one for rural areas. The population attributable fraction for PAT was calculated [18].

Variables with P values <0.25 were introduced simultaneously in each of the final models, and removed one by one until all variables left in the models had P values <0.05. In the final model, in order to keep in the same model all observations (males and females), a new variable was created with three categories: males, circumcised females, and uncircumcised females. However, to assess the extent of confounding in the association between female circumcision and HCV infection, age-adjusted and multi-adjusted ORs were also compared in models including women only. To account for the dependence of observations belonging to the same clusters, generalised estimated equations (GEE) models were used [19,20], assuming an exchangeable working correlation inside the clusters. For variables with ordered categories, a test for trend was also performed. All analyses were performed using the R statistical software [21].

RESULTS

Of 12 780 eligible subjects aged 15–59 years, 11 126 (87.1%) agreed to participate and provided a blood sample. HCV antibody prevalence was 14.7% (95% CI 13.9–15.5%) in the 15–59 years old age group. Prevalence was highest (17.5%) in Lower Egypt (the Nile Delta), followed by Upper Egypt (14.7%), Urban Governorates (Cairo, Alexandria, Port Said and Suez) (9.5%), and Frontier Governorates (3.8%) (Fig. 1). HCV antibody prevalence gradually increased with age, reaching, in the 50–59 years age group, 46.3% and 30.8% in males and females, respectively. It was higher in males compared to females (17.4% versus. 12.2%, respectively, $P < 0.001$), and in rural compared to urban areas (18.0% vs. 10.3%, respectively, $P < 0.001$) (Fig. 2). Among participants with positive HCV antibody, 1064/1571 (67.7%) were viremic. The proportion of viremic subjects was higher among males compared to females (69.9% versus. 65.1%, respectively; $P = 0.04$). There was no difference in the proportion of viremic according to age, or type of exposure.

The HCV antibody prevalence decreased with increasing level of education and wealth, whereas it increased with the number of people living in the household (Table 1). A past history of blood transfusion, of PAT, of unsafe injection, and female circumcision were all associated with HCV infection in univariate analysis. A past history of surgery, dental treatment, and caesarean section were not associated with HCV infection (Table 1). There was no significant interaction between these factors and age group (age above or under 30) or sex. However, the effect of past history of PAT, of female circumcision, and of lack of education, on HCV risk was stronger in urban when compared to rural areas (Table 2). The increased risk associated with circumcision in

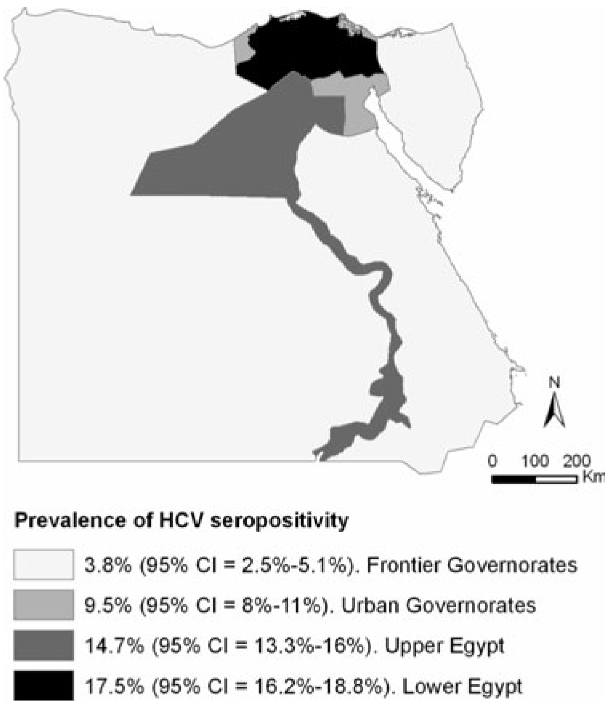

Fig. 1 HCV antibody prevalence (%) by major subdivision, Egypt DHS 2008.

females living in urban areas persisted (aOR = 5.18, 95% CI 1.91–21.23) even after removing the 231 women who reported migrating from a rural to an urban area. Also, there was no increase in risk of HCV infection whether the person who performed the circumcision came from the informal (e.g., traditional midwife) as opposed to the formal health sector, whether it was in rural (aOR = 1.13, 95% CI 0.83–1.55) or in urban (aOR = 1.20, 95% CI 0.80–1.86) areas.

The population attributable risk of PAT for HCV infection for participants aged 30–59 years was 11.0% in urban areas, and 7.8% in rural areas. Removing migrants from the analysis did not substantially modify any of the ORs displayed in Table 2 (data not shown).

In multivariate analysis (Table 3), in urban areas, age, male sex, past history of PAT, lack of education, poverty, and residence outside the Frontier Governorates were associated with increased risk of HCV infection. Being noncircumcised for females was associated with a decreased risk of infection, independently of all above factors in urban areas. To assess the extent of confounding that may exist in the relationship between female circumcision and HCV infection, a multivariable model including women only was built and showed limited (4.9%) changes in the age-adjusted (4.32) and the multi-adjusted (4.12) OR in urban areas. In that same model, the effect of female circumcision significantly differed in urban (aOR = 4.12, 95% CI 1.29–13.2) and rural areas (aOR = 0.75, 95% CI 0.40–1.40) (P-value for the test of interaction = 0.004). In rural areas, age, male sex, past history of PAT, poverty, blood transfusion, and living outside of the Frontier Governorates were all independently associated with an increased risk of HCV infection.

DISCUSSION

This survey represents the first estimate of HCV antibody prevalence in Egypt using a large and representative sampling of the entire population. The overall finding, 14.7% prevalence in the 15–59 years age group, confirms the severity of the epidemic as anticipated from previous community-based surveys [1].

This overall figure hides some important disparities, the first being the higher prevalence observed in rural (18.0%) when compared to urban (10.3%) areas, in relation with the founding event of the epidemic, i.e. the mass anti-schistosomiasis treatment campaigns. Between 1964 and 1982, an estimated 2 million Egyptians, in majority children above 5

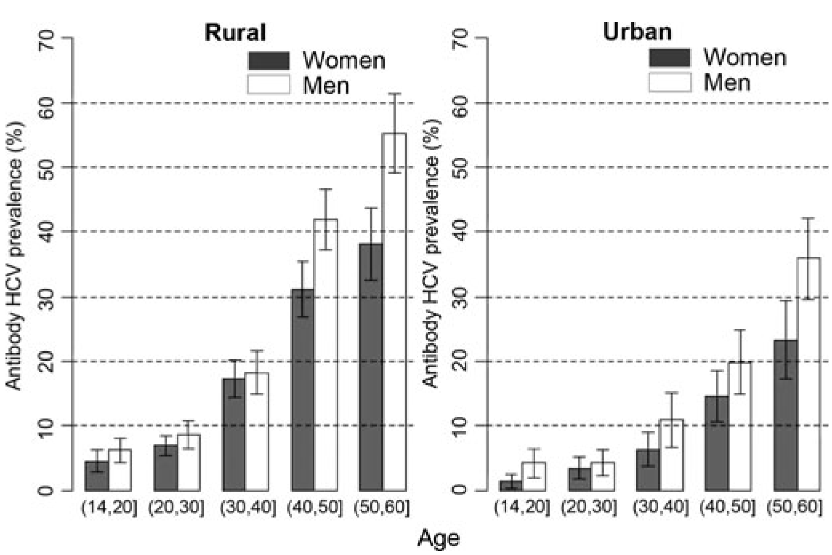

Fig. 2 HCV antibody prevalence by age, sex, and urban/rural area, Egyptian DHS 2008 (rural: women: n = 3666; men: n = 3012/urban: women: n = 2386; men: n = 2062).

Table 1 Factors independently associated with HCV antibody in univariate analysis, Egyptian DHS 2008

Risks factors	Number (%) exposed	Number of HCV antibody positive (%*)	Age-adjusted OR (95% CI)	Age-adjusted *P*-value
Major subdivisions				
Frontier Governorates	625 (5.6)	23 (3.8)	1	
Lower Egypt	4309 (38.7)	744 (17.5)	5.55 (3.68–8.79)	<0.001
Upper Egypt	4614 (41.5)	652 (14.7)	4.54 (3.01–7.20)	<0.001
Urban Governorates	1578 (14.2)	152 (9.5)	2.38 (1.53–3.85)	<0.001
Missing	0			
Type of area				
Rural	6678 (60.0)	1129 (18.0)	1	
Urban	4448 (40.0)	442 (10.3)	0.45 (0.40–0.51)	<0.001
Missing	0			
Gender				
Women	6052 (54.4)	711 (12.2)	1	
Men	5074 (45.6)	860 (17.4)	1.51 (1.35–1.69)	<0.001
Missing	0			
Blood transfusion				
No	10634 (95.8)	1466 (14.3)	1	
Yes	468 (4.2)	101 (24.3)	1.31 (1.02–1.66)	0.029
Missing	24			
Parenteral treatment for schistosomiasis				
No	9952 (90.8)	1249 (13.2)	1	
Yes	1006 (9.2)	288 (29.5)	2.00 (1.70–2.35)	<0.001
Missing	168			
Injection unsafe				
No	9666 (96.4)	1378 (14.8)	1	
Yes	359 (3.6)	77 (20.6)	1.34 (1.01–1.76)	0.036
Missing	1101			
Female circumcision†				
No	503 (8.3)	16 (3.8)	1	
Yes	5544 (91.7)	695 (12.8)	2.61 (1.61–4.54)	<0.001
Missing	5			
Use of water pipe				
No	10638 (95.7)	1465 (14.4)	1	
Yes	474 (4.3)	103 (21.5)	1.27 (1.00–1.6)	0.050
Missing	14			
Educational attainment				
Complete secondary or higher	4868 (43.8)	506 (10.5)	1	
Incomplete secondary or less	3661 (32.9)	486 (13.9)	1.24 (1.08–1.43)	0.002
No education	2597 (23.3)	579 (24.0)	1.37 (1.19–1.58)	<0.001
Missing	0			
Wealth index quintile				
Poorest	2230 (20.0)	377 (18.6)	1	
Poor	2473 (22.2)	394 (17.1)	0.87 (0.74–1.02)	0.094
Middle	2332 (21.0)	366 (16.4)	0.85 (0.72–1.01)	0.066
Rich	2015 (18.1)	228 (11.6)	0.51 (0.43–0.62)	<0.001
Richest	2076 (18.7)	206 (10.2)	0.42 (0.34–0.50)	<0.001
Missing	0			
Number of people in the household				
[1.4]	3264 (29.3)	411 (12.9)	1	
(4.6]	3962 (35.6)	592 (15.5)	1.23 (1.07–1.43)	0.004
(6.7]	1228 (11.0)	194 (15.9)	1.40 (1.15–1.70)	0.001
(7.39]	2672 (24.0)	374 (15.4)	1.32 (1.13–1.55)	0.001
Missing	0			

*Weighted percentages. †Females only.

Table 2 Factors associated with HCV infection showing interaction by urban/rural residence, Egyptian DHS 2008*

Risks factors	Number (%) exposed	Number of HCV antibody positive (%)	Age-adjusted OR (95% CI)	Age-adjusted *P*-value
Urban				
Parenteral treatment for schistosomiasis				
No	4153 (95.1)	368 (8.9)	1	
Yes	212 (4.9)	63 (29.7)	2.94 (2.09–4.10)	<0.001
Female circumcision				
No	335 (14.0)	4 (1.2)	1	
Yes	2051 (86.0)	181 (8.8)	4.32 (1.78–14.22)	0.005
Educational attainment				
Complete secondary or higher	2479 (55.7)	193 (7.8)	1	
Incomplete secondary or less	1399 (31.5)	131 (9.4)	1.11 (0.87–1.41)	0.410
No education	570 (12.8)	118 (20.7)	1.64 (1.25–2.15)	<0.001
Rural				
Parenteral treatment for schistosomiasis				
No	5799 (88.0)	881 (15.2)	1	
Yes	794 (12.0)	225 (28.3)	1.50 (1.24–1.80)	<0.001
Female circumcision				
No	168 (4.6)	12 (7.1)	1	
Yes	3493 (95.4)	514 (14.7)	1.26 (0.71–2.45)	0.466
Educational attainment				
Complete secondary or higher	2389 (35.8)	313 (13.1)	1	
Incomplete secondary or less	2262 (33.9)	355 (15.7)	1.09 (0.92–1.30)	0.328
No education	2027 (30.4)	461 (22.7)	0.90 (0.75–1.07)	0.226

*P-value of the test of interaction: parenteral treatment for schistosomiasis: $P < 0.001$, female circumcision: $P = 0.026$, educational attainment: $P < 0.001$

years of age and young adults, received antimony salts in series of intravenous injections with insufficiently sterilised needles [1]. In this survey, performed 30 years after the end of the treatment campaigns, the proportion of HCV infections attributable to PAT among participants older than 30 years of age was estimated at 7.8% and 11.0% in rural and urban areas, respectively. Others may have been infected from this initial pool through various modes of transmission, which unfortunately could not be explored thoroughly in this study. The lack of detailed questionnaire, and the inclusion of prevalent rather than incident cases due to the cross-sectional nature of the survey, did not allow a rigorous 'risk factor' analysis. Other recent studies using incident cases have shown that medical injections in both rural and urban areas, surgery, gum treatment, and intravenous illicit drug use in urban areas, are important current modes of HCV transmission in Egypt [22–24] and should be targeted by intensive infection prevention campaigns.

The second important finding of this study is the higher prevalence observed among males. In subjects older than 30 years of age, this difference may be partly related to the higher exposure of males to the past anti-schistosomiasis treatment campaign. Indeed, in this age group, past history of treatment was found in 516/2128 = 19.5% and 198/2818 = 6.6% of males and females, respectively. It does not account for the whole difference though, since the increased risk in males remained after adjustment for anti-schistosomiasis treatment in multivariate analysis, and was observed among the <30 years who were not exposed to anti-schistosomiasis treatment. It may be related to another sex-specific exposure not assessed in this study, or a higher susceptibility of males to infection as already suggested by others [25].

Another important finding was the trend for HCV antibody prevalence to be lower with increasing wealth. This is the first time in any resource-limited country that such assessment of the relationship between HCV infection status and wealth could be performed at the national level, using the DHS wealth index based on assets and services held by the household [17]. It was not obvious a priori that wealthier subjects would be less affected by the epidemic, since higher wealth might have been associated with more frequent access to health care, hence exposure to HCV infection. The type of health care serving the poorest segments of the population, and the likelihood of re-use of unsterilized material in this context, might explain the observed relationship, but could not be assessed in this study.

Lack of education was associated with increased risk in urban, but not in rural areas. It reflects in part the fact that in rural areas, the background HCV circulation is so high

Table 3 Multivariate analysis of factors associated with HCV infection by urban/rural residence, Egyptian DHS, 2008 (n = 4356 for urban and 6578 for rural areas)

	Urban		Rural	
Exposure	Adjusted OR 95% CI	Adjusted *P*-value	Adjusted OR 95% CI	Adjusted *P*-value
Age	1.07 (1.06–1.09)	<0.001	1.08 (1.07–1.09)	<0.001
Gender and circumcision*				
Female circumcised	1		1	
Female not circumcised	0.25 (0.09–0.75)	0.013	1.42 (0.78–2.60)	0.256
Male	1.73 (1.37–2.18)	<0.001	1.40 (1.21–1.62)	<0.001
Parenteral treatment for schistosomiasis				
No	1		1	
Yes	2.54 (1.83–3.52)	<0.001	1.33 (1.10–1.59)	0.003
Blood transfusion				
No	1		1	
Yes	1.37 (0.94–2.01)	0.104	1.44 (1.04–2.00)	0.029
Educational attainment†				
Complete secondary or higher	1		1	
Incomplete secondary or less	1.03 (0.77–1.36)	0.863	1.07 (0.88–1.29)	0.498
No education	1.70 (1.22–2.36)	0.002	0.96 (0.77–1.20)	0.710
Wealth index quintile‡				
Poorest	1		1	
Poorer	0.57 (0.29–1.12)	0.105	0.89 (0.71–1.10)	0.275
Middle	0.64 (0.35–1.17)	0.145	0.88 (0.70–1.11)	0.274
Richer	0.50 (0.27–0.91)	0.024	0.63 (0.45–0.87)	0.005
Richest	0.48 (0.26–0.90)	0.022	0.73 (0.52–1.03)	0.074
Major subdivisions§				
Frontier Governorates	1		1	
Lower Egypt	3.01 (1.69–5.36)	<0.001	9.36 (4.55–19.26)	<0.001
Upper Egypt	2.45 (1.36–4.40)	0.003	6.35 (3.08–13.07)	<0.001
Urban Governorates	2.31 (1.30–4.09)	0.004		

* Global test: urban: $P < 0.001$/rural: $P < 0.001$. † Test for trend: urban: $P = 0.006$/rural: $P = 0.72$. ‡ Test for trend: urban: $P = 0.03$/rural: $P = 0.01$. § Global test: urban: $P = 0.002$/rural: $P < 0.001$.

that, relative to any baseline 'non-exposed' category, increases in risk related to exposures tended to be less pronounced. In a previous case control study performed in Cairo, lack of education was also strongly associated with HCV infection [22,24]. It is conceivable that lack of knowledge about HCV transmission routes among the least educated subjects puts them at risk of infection.

The last intriguing finding was the lowest risk of infection observed among uncircumcised women when compared to circumcised women, although this finding was seen only in urban areas. Since HCV antibody prevalence was only 1/278 = 0.3% among females aged <18 years in urban areas, and since circumcision is performed before that age [26] the procedure itself cannot explain the increased risk among the circumcised at least at the present time. Whether the increased prevalence reflects past transmission during female circumcision at a time hygiene standards were lower cannot be excluded based on the data available. It may also reflect the protective effect of the higher socio-economical status of uncircumcised women, not fully controlled for by the crude indicators used in the multivariate analysis.

Altogether, the main lesson from this study is the confirmation of the severity of the HCV epidemic in Egypt. HCV infection has a long incubation period, so that the peak morbidity and mortality is still to come [27]. Among these individuals with positive antibodies, 67.7% were viremic, and may develop complications of chronic infection if not already done. Of note, as described before [28,29], we found that females had lower rate of viremia compared to males, this time at the national level. The reasons for better HCV clearance in females remain uncertain.

Egypt is now facing two main challenges to control the HCV epidemic, one with prevention, and one with care provision. Recent studies have documented on-going HCV transmission in Egypt, as shown by incidence rates ranging from 0.8 to 6.8 per 1000 person-years in three Egyptian villages [23,30], with health care-related procedures as the main routes of current HCV transmission [22–24]. On-going efforts to provide disposable material, or promote adequate sterilisation procedures, to all health facilities should be strengthened. What this study adds is the evidence for increased vulnerability of the poorest and least educated segments of the population. As a result, educational efforts should target the underpriviledged, sensitizing them to the risks associated with contact with infected blood, and making them critical actors in prevention, by allowing them to make educated choices about safer treatment procedures.

The other main challenge will be to provide treatment programmes, at affordable costs, to the many individuals in need, particularly if the disease is among the poorest. In 2008, the Egyptian Ministry of Health launched an integrated National Control Strategy, including the opening of 20 national treatment reference centres providing pegylated interferon and ribavirin for free to those with national health insurance (50% of treated patients) or who cannot pay (40% of treated patients). This is a major achievement, the sustainability of which will largely depend on the cost of treatment. Local and international initiatives to bring down the cost of anti-hepatitis treatments for developing countries, similar to those which decreased by 100-fold the cost of antiretroviral therapies, are urgently required.

ACKNOWLEDGEMENTS

The authors would like to thank El Zatany and associates, working on behalf of the Ministry of Health and Population in Egypt, who implemented the study together with ICF Macro. The authors would also like to thank the Measure DHS initiative for making these data available for analysis and publication.

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