Epidemic hepatitis C virus infection in Egypt: estimates of past incidence and future morbidity and mortality

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SUMMARY. Hepatitis C virus (HCV) infection is gaining increasing attention as a global health crisis. Egypt reports the highest prevalence of HCV worldwide, ranging from 6% to more than 40% among regions and demographic groups. Predicting the impact of the epidemic has been difficult because of the long-latency period and low-resource setting. Accordingly, we sought to estimate historic incidence and predict the future impact of HCV using Markov simulation modelling techniques. Age-specific HCV incidence rates (IRs) were estimated using previously acquired age-specific HCV prevalence data. Data for this analysis were from a highly detailed, community-based seroprevalence study from 2003. Future HCV-related morbidity and mortality were estimated using a computer cohort simulation of HCV natural history in the Egyptian population. Population and natural history parameters were defined using results from a meta-analysis and existing comprehensive literature reviews. Incidence model estimates ranged from 2.01 to 25.47 HCV cases per 1000 person-years (PYs). The highest IRs were calculated among those over 35 years of age. Our Markov model predicted 127 821 deaths from chronic liver disease and 117 556 deaths from hepatocellular carcinoma in Egypt over the next 20 years. During this period, it was estimated that HCV would yield 750 210 PY of decompensated cirrhosis, 132 894 PY of hepatocellular carcinoma, and a total loss of 32.86 million years of life compared to a non-infected cohort. Our results support the claim of high HCV incidence in Egypt and suggest that HCV may lead to a substantial health and, consequently, economic burden over the next 10–20 years.

Keywords: developing countries, indirect incidence, infectious disease, liver cancer, Markov model.

INTRODUCTION

Hepatitis C virus (HCV) infection is gaining increasing attention as a global health problem, with approximately 3% of the world's population infected [1,2]. These individuals are at greater risk for developing cirrhosis and/or hepatocellular carcinoma (HCC). Egypt reports the highest prevalence of HCV worldwide, ranging from 6% to more than 40% with an average of 13.8% [3–5]. In populations of blood transfusion recipients over the age of 30, this proportion has been reported to be as high as 73%, and in the general population aged 40–60 years it can be as high as 55%. At the same time, the prevalence in children is much lower, ranging between 2% and 10% [3–5]. While the levels in children are much lower than those seen in the older population, they are still excessive by World Health Organization (WHO) standards, where prevalences greater than about 3–4% are considered high [2].

In Egypt, the major route of exposure to HCV appears to have been via widespread parenteral antischistosomal treatment (PAT), with more than 35 million injections given over a 20-year period (1960–1980) [3]. Despite termination of this program and the implementation of measures designed to reduce hospital-related infection, transmission continues.

Because the prevalence of HCV is exceeding that of HBV infection, HCV infection has become the leading risk factor for HCC in Egypt (antibodies present in as many as 75–90% of HCC cases) [6]. The frequency of liver-related cancers (>95% as HCC) relative to all cancers in Egypt has increased from approximately 4.0% in 1993 to 7.3% in 2003 [7]. Now the second highest cause of cancer incidence and mortality among men, HCC in Egypt occurs at rates significantly greater than those seen in surrounding Middle Eastern countries, as well as in the USA [8].

Incidence data are limited, however, because researchers have been plagued by logistical and methodological difficulties. Initial infection is rarely symptomatic, and chronic

Abbreviations: HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HBV, hepatitis B virus; IR, incidence rate; PY, person-years; yo, years old.

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carriage is insidious. Thus, it is important to characterize the HCV situation in Egypt to predict the future health burden and guide appropriate health policy to confront the issue.

Various mathematical techniques provide practical approaches for making reasonable estimates about the history of the HCV epidemic and future predictions of HCV-related morbidity and mortality. Methods for indirectly calculating age-specific incidence rates (IRs) using seroprevalence data were developed during the 1980s [9–11]. Saidel *et al.* [12] successfully validated one of these methods for HIV by comparing its predictions with observations from an incidence study. Such a method is advantageous, as it uses data from a single cross-sectional survey to estimate incidence and is particularly appropriate for developing countries where incidence data are frequently unavailable or unreliable.

The purpose of this study was to provide quantitative estimates of the burden of HCV infection among Egyptians. Burden was measured in two ways: First, we examined the burden of past infection incidence to further probe the hypothesis that the PAT campaign was largely responsible for the present epidemic in Egypt and shed light on the resulting epidemic curve, applying indirect estimates of historical IRs using seroprevalence data. Second, we used a Markov natural history model to estimate the impact of this epidemic, measured as future morbidity and mortality from sequelae of chronic HCV infection.

MATERIAL AND METHODS

Prevalence and population data

Age- and sex-specific population and mortality data for 5-year age groups were obtained from Egypt's Central Agency for Public Mobilization and Statistics (CAPMAS) and the WHO [13,14].

Prior systematic review of the literature identified high quality HCV prevalence studies for the period 1992–2005 [15]. Briefly, we selected five studies from the period 2001–2002, which we considered to have the greatest amount of detail and the highest methodological quality [4,16–19]. All studies were conducted on large ($n > 1400$) apparently healthy community-based populations. Third generation ELISA was used in all cases to test for HCV antibody. These studies covered ages 5–60+ years as well as geographic regions of interest (Upper and Lower Egypt). Since it is known that prevalence varies significantly between children and adults as well as between Upper and Lower Egypt, this sample of studies is highly representative of Egypt when considered in aggregate.

Age-specific prevalences across studies were compared using the chi-square test to determine if pooling results would be appropriate. No significant differences were found among adults from Lower Egypt, children from Lower Egypt, adults from Upper Egypt, or children from Upper Egypt. Summary age-specific prevalence measures, as well as male:female ratios from these studies, were calculated as weighted averages using a standard method [20]. The individual prevalence for each study was multiplied by the corresponding sample size and divided by the total (pooled) sample size of all studies. To populate the initial values of the HCV Infection health state in the Markov model, these summary age-specific prevalence proportions (adjusted for sex) were multiplied by their respective census population values.

Incidence rate estimates

The method for estimating age-specific IRs from prevalence data was originally described by Leske *et al.* [9], Podgor *et al.* [10] and Podgor and Leske [11]. Although initially developed for studying glaucoma, Saidel *et al.* [12] tested model predictions against observed incidence for HIV/AIDS and determined the model can provide crude estimates of 1-year age-specific IRs that are similar to those observed in longitudinal studies of HIV/AIDS. For these calculations, we chose to select only one of the studies mentioned above, so as not to introduce bias. Since we are inferring incidence measures, it is best not to pool studies where HCV seroprevalence was measured by different researchers on different populations. This decision was made in the interest of preserving internal validity at the expense of external validity and the ability to generalize results beyond the specific study population of interest. We chose to focus our investigation of incidence on the data from Arafa *et al.* [18], which presents age-specific prevalence from an area in Lower Egypt, the region known to have higher levels of HCV in Egypt [17].

Incidence rates are derived by using estimated prevalence of disease at the beginning and end of an age interval and the known age-specific mortality rates during the interval. The model is based on the functional relation between a risk (CI) and a rate (ID) as:

$$\text{CI} = 1 - e^{-(\text{ID} \times \Delta t)}$$

where ID is incidence density, CI is cumulative incidence, and Δt is the elapsed time (which could be defined by age differences), as long as the assumption of constant incidence within a time interval is not violated [12]. After accounting for age-specific mortality within age intervals, Leske *et al.* [9] propose the following:

$$I_x = \frac{\ln(1 - \Pi_x)}{\ln(1 - q_x) + \ln(1 - \Pi_x)} \times \frac{1 - (1 - \Pi_x)(1 - q_x)}{(1 - 1/2q_x)}$$

where I_x is the incidence rate for the age interval; q_x the probability of dying during the age interval; $x + 1$ = age interval immediately following x

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

where P_x is the prevalence proportion at the beginning of the interval.

After solving for I_x, it is divided by the number of years in the age interval to estimate the mean annual rate for time interval x. In 1983, Podgor *et al.* validated this model against other, more established methods [10]. For more details on the derivation and validation of this method, see Refs. [9–12]. Variance and standard error for model estimates were calculated using the 'delta method' described by Armitage and Leske [9,21], respectively, as:

$$\text{Var}(I_x) = [\partial I_x / \partial \Pi_x]^2 \text{Var}(\Pi_x)$$

To use this model, it is necessary to address the following three assumptions:

1. *Infection is lifelong and irreversible.* We limit our analysis to chronically infected individuals, as the rate of remission is quite low. In addition, treatment for HCV in Egypt is limited and rarely successful in eliminating infection.
2. *Homogeneity within age intervals.* This model assumes mortality rates, disease IRs and population risk factors remain constant within the age intervals of analysis. We restricted age intervals to 5-year periods, making it reasonable to assume homogeneity of these characteristics within age categories.
3. *Non-differential mortality rates between HCV+ and HCV– individuals.* Model estimates using this method are not robust when one age interval is followed by another with lower prevalence (results in a negative incidence) [12]. For the purpose of this analysis, therefore, age groups >50-years old (yo) were excluded, because prevalence levels begin to decline. Truncating this analysis to those <50 yo is reasonable, since the purpose is to identify recent incidence trends following the elimination of the PAT campaign, making younger age groups more relevant. Adjusting for differential mortality due to cirrhosis/ liver failure/HCC would be essential in populations >50 yo, but it is negligible in younger groups. Differential mortality is the result of long-term sequelae associated with chronic HCV infection. Previous work has shown that these sequelae have their greatest impact in the population over 50 yo and have little effect in younger individuals [6–8,22]. However, access to cirrhosis and other non-HCC liver disease mortality data was extremely limited despite extensive searching. In our own sensitivity analyses, we found the estimates to be fairly stable in the presence of varying mortality rates. Thus, because we limited age groups to <50 yo, no adjustment for differential mortality was needed.

Future HCV-related morbidity/mortality

Using Visual Basic for Microsoft Excel™, we developed a Markov simulation model to predict HCV-related morbidity and mortality among a cohort representative of the HCV-infected population in Egypt (Fig. 1; Table 1). Cohort mem-
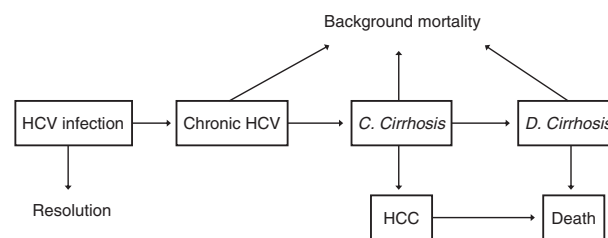

Fig. 1 Natural history model for Hepatitis C virus infection and its sequelae. Conceptual model showing the health states incorporated into the Markov simulation model. C, compensated; D = decompensated.

bers move among health states over 1-year time steps for 20 years. By tracking the proportion of the cohort developing sequelae, we were able to estimate the future health burden. The likelihood of health state transitions was based on probabilities derived from a review of the literature as well as publications from the WHO Hepatitis C Working Group (Table 1; the literature used to guide parameter estimates is cited in Appendix 1). The initial HCV Infection Health state was populated using the summary age-specific prevalence proportions discussed above and multiplying them by their respective census population estimates.

The model is set up to include ages 0–80 (time step = 1 year). Anyone alive at age 80 years dies by age 81. Since life expectancy in Egypt is 69 for males and 73 for females, and the population over 80 years of age accounts for only 0.3% of the total population, this age structure seems reasonable [14]. To incorporate aging into the model, we added the probability of remaining in a healthy state from one time step to the next, which is simply [1 – sum(transition probabilities to different health states)]. This exists for all health states except the original HCV infection. No one remains in the HCV infection health state after the first time step, when people are either moved to chronic infection, or removed from the system in the resolution health state.

Age- and sex-specific background mortality rates were obtained from the WHO and are applied to the following health states: chronic HCV infection, compensated cirrhosis, and decompensated cirrhosis [14]. All deaths from hepatocellular carcinoma are considered to be attributed to it. No deaths occur in the first time step. Typically, hepatitis C infection resolves or becomes chronic within the first year of infection [1,2]. Since our prevalence estimates are population-based, the first time step is designed to appropriately calculate the number of chronically infected individuals.

Sex is incorporated only insofar as generating the initial population structure and applying age-sex-specific background mortality. Although we hypothesize that transition probabilities may indeed be different by sex, they have yet to be clearly defined in the literature and from prospective cohort studies. Since previous research has indicated a

Table 1 Health state transition probability estimates used in the Markov simulation

Health state (*i*)	Health state (*i* + 1)	Annual probability	Lower bound	Upper bound
HCV infection	Chronic infection	0.75	0.50	0.85
	Infection resolution	1-P(Chronic)		
Chronic infection	Compensated cirrhosis*	0.05/20 (<40 years)	N/A	N/A
	Background mortality†	0.20/20 (40+ years)		
Compensated cirrhosis	Decompensated cirrhosis			
	Hepatocellular carcinoma	0.065	0.04	0.092
	Background mortality†	0.035	0.024	0.046
Decompensated cirrhosis	Death from D cirrhosis			
	Background mortality†	0.186	0.137	0.300
Hepatocellular carcinoma	Death from HCC‡	0.95		

Upper and lower bound estimates for sensitivity analysis were determined based on error associated with parameter estimates found in the literature.
*The compensated cirrhosis transition probability is 0.05 over 20 years if the individual was initially infected with HCV prior to 40 years of age. The transition probability is 0.2 over 20 years if the individual was aged 40 years or older at the time of initial HCV infection (Appendix 1). †Background mortality is defined by age-sex-specific rates obtained from WHO [14]. ‡All death from hepatocellular carcinoma is assumed to be attributed to it.

greater proportion of males are infected in Egypt *vs* females, sex is included to reflect these different initial values [3–7,16–19]. For the Markov model alone, it provides little beyond the initial values and the ability to project sex-specific health outcomes.

The disability or mortality burdens related to HCV infection were estimated. We used the computer simulation to determine the years of life spent by the cohort with decompensated cirrhosis or hepatocellular carcinoma (HCC). To estimate the years of life lost, we also compared life expectancy estimates for the chronic HCV population with those for an age- and sex-matched general population. These estimates calculated premature mortality and assumed permanent disability once patients developed decompensated cirrhosis or HCC, but did not consider quality-of-life deficits, as no such studies have been reported from Egypt that would provide appropriate quality of life information for HCV infection. The model was limited to 20 years because: (1) the natural history beyond 20 years is less certain, weakening our confidence in parameter estimates; and (2) estimates of disease and death are less meaningful, as they would not include incident cases who became infected during the period of analysis (due to the unavailability of incidence data).

RESULTS

Age-specific prevalence

All studies used in calculating summary measures had sample sizes greater than 1400, reducing the probability of bias in prevalence estimates due to low power. Chi-square tests revealed no significant differences between studies measuring redundant populations (i.e. adults from Lower Egypt), so summary measures for the natural history model were calculated (not shown).

Summary prevalence estimates were calculated for the following age groups: 5–9, 10–14, 15–19, 20–29, 30–39, 40–49, and 50+. As expected, prevalence consistently increased with age except for a decrease between the age groups 40–49 and 50+. The decrease in the final age group could be related to lower past exposure to HCV through PAT which is tightly linked to HCV infection. Pooled estimates also revealed a male:female ratio of 1.2:1 for ages 0–19 years and 1.6:1 for individuals ≥20.

Incidence rate estimates

Raw prevalence measures used in the calculation of IRs [18] were smoothed by fitting them to a logistic curve ($1/e^{(a - bx)}$), where $a = -4.172$ and $b = -0.076$ (Fig. 2). Table 2 presents the results from the age-specific IR calculations. Mean annual IRs were obtained by dividing the model estimate by the number of years included in the age interval (5 years). Model estimates ranged from 2.01 to 25.47 per 1000 PY. The highest IRs were calculated for those ≥35 yo. Such high incidence for these people is consistent with the age cohort effect seen with respect to the PAT campaign. We were unable to estimate the IRs for those ≥50 yo, because prevalence significantly decreases beginning with the 55–59 yo age group. This particular method for estimating incidence loses accuracy under these conditions and frequently results in the calculation of a negative IR.
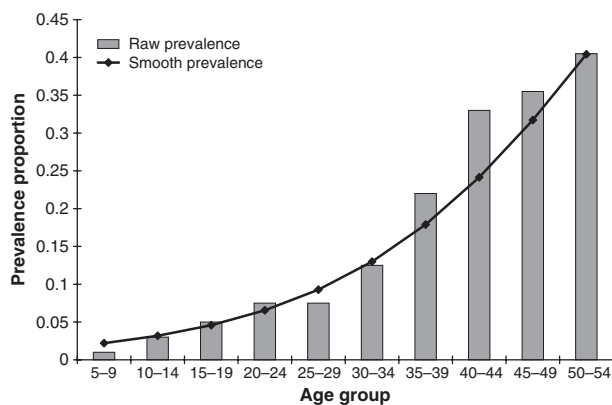
Fig. 2 Raw age-specific HCV prevalence proportions in Lower Egypt, 2002. Data from Arafa *et al.* [18] were used and plotted with smoothed age-specific prevalence estimates. Prevalence data were fit to a logistic curve: $1/e^{(-a-bx)}$ where $a = -4.172$; $b = -0.076$.

Future HCV-related morbidity and mortality

Predictions from the Markov model that estimate future HCV-related morbidity and mortality in Egypt, including the upper and lower bound estimates from sensitivity analysis, are striking (Table 3). Based on review of the prevalence studies, approximately 8.84 million individuals (4.98 million males and 3.86 million females) are estimated to be infected with HCV in Egypt, resulting in 6.62 million with chronic infection. Our model predicted that over the next 20 years a total of 127 821 deaths due to decompensated cirrhosis would occur in this cohort, plus another 117 556 deaths due to HCC. The highest proportion of deaths related to HCV

will occur 10–20 years from now. Deaths due to HCC appear to peak within 15–16 years, whereas deaths due to decompensated cirrhosis only begin to flatten out in the final 2 years of analysis (Fig. 3). Deaths from HCC are greater than deaths from decompensated cirrhosis earlier in the model, due to the fact that individuals diagnosed with HCC in Egypt typically do not live past 1 or 2 years, whereas people with decompensated cirrhosis can live several years before succumbing to the condition.

In addition to the 244 377 HCV-related deaths predicted by the model, when compared with an age-matched general population over the same time period, the HCV-infected cohort would have accumulated 3 862 643 years of compensated cirrhosis, 750 210 years of decompensated cirrhosis, 132 894 years of hepatocellular carcinoma, and the loss of 32.86 million years of life.

DISCUSSION

The objective of this study was to estimate past incidence of HCV using an indirect method and make projections about the future health burden using a natural history model. Despite Egypt's status as the country with the highest levels of HCV infection in the world, few studies have been done to characterize the dynamics of transmission, how they may have changed over time, and what this means for the future of health in Egypt. There is little doubt that the HCV epidemic is largely the result of some health care workers using unsterilized needles during the PAT campaign between the 1960s and the 1980s [3,6,23,24]. Beyond identifying PAT as the dominant source of infection, however, little research has been undertaken to characterize HCV dynamics and public health implications. Prevalence

Table 2. Indirectly estimated age-specific incidence rates for HCV in Lower Egypt

Age group (years)	Prevalence (%) [Raw]	Prevalence (%) [Smooth]	Incidence (SE)	Mean annual incidence per 1000 PY
5–9	1.0	2.2	0.010 (0.01)	2.01
10–14	3.0	3.2	0.014 (0.01)	2.89
15–19	5.0	4.6	0.021 (0.01)	4.13
20–24	7.5	6.5	0.029 (0.01)	5.85
25–29	7.5	9.3	0.041 (0.03)	8.19
30–34	12.5	13.0	0.056 (0.03)	11.28
35–39	22.0	17.9	0.076 (0.04)	15.21
40–44	33.0	24.1	0.010 (0.05)	19.99
45–49	35.5	31.7	0.127 (0.06)	25.47
50–54	40.5	40.4	–	–
55–59*	32.0	49.8	–	–
60+*	22.5	59.1	–	–

Incidence rates were calculated using smoothed age-specific prevalence measures. Data were fit to a logistic curve: $1/e^{(a-bx)}$ where $a = -4.172$; $b = -0.076$.*Not included in incidence calculations to preserve integrity of the smoothed prevalence estimates.

Table 3 Predicted HCV-related morbidity and mortality

Health state	Estimate	Lower bound	Upper bound
Compensated cirrhosis (life years)	3 862 643	2 902 917	3 881 476
Decompensated cirrhosis (life years)	750 210	392 042	818 895
Hepatocellular carcinoma (life years)	132 894	68 132	176 333
Decompensated cirrhosis (deaths)	127 821	48 728	227 701
Hepatocellular carcinoma (deaths)	117 556	59 960	156 713

Estimates were measured as life years or number of deaths. Upper and lower bound estimates were obtained by varying parameter estimates in accordance with their margin of error as indicated by the literature.
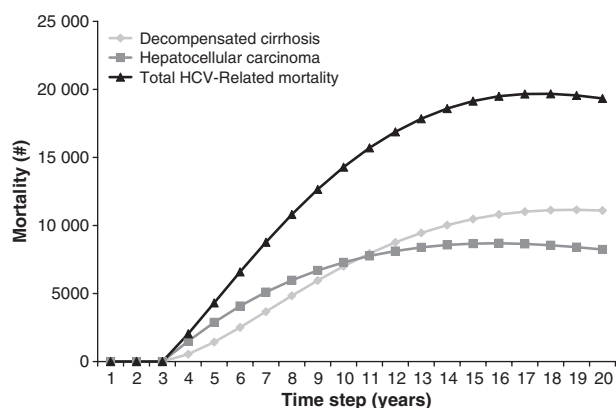

Fig. 3 Future HCV-related morbidity and mortality in Egypt. Predicted mortality due to HCV-related decompensated cirrhosis and hepatocellular carcinoma over a 20-year period.

studies show a significantly lower level of HCV infection among younger individuals, with rural populations approximately 12% and urban areas at only 2–3% [3,4,16–19]. This still exceeds the WHO's definition of high endemicity (4%), leaving Egypt's position as a leading country in the burden of HCV unchanged. Recent cross-sectional studies have found little evidence that formal medical procedures still contribute to transmission. In addition, informal medical procedures, such as circumcision performed by a barber, show significant associations but can only explain between 10% and 20% of the infections [3,4,6]. Some have suggested that intra-familial transmission may be crucial in transmission, but this hypothesis has yet to be specifically tested [25–27]. Although illuminating, such reports do not help with inferences regarding the future of HCV, and consequently the future of liver disease, in Egypt.

Incidence estimates

To address this knowledge gap, we calculated past age-specific HCV IRs using a method that analyses HCV prevalence data from a one-time, cross-sectional survey. Although originally developed for studying chronic diseases like glau-

coma, Saidel *et al.* [12] demonstrated the validity of this method when compared with observational data from a HIV/AIDS study. As expected, we identified very high IRs among those ≥30 yo. Among those <30 yo, largely comprised of people unaffected by the PAT campaign, we noted a continuous decline in IRs. Despite lower incidence among those 5–14 yo, IRs remained at 2–3 per 1000 PY, suggesting that transmission to children must still be occurring despite the elimination of PAT and intense measures to reduce other iatrogenic exposures. Future longitudinal studies are needed to gather observational data both to validate these findings as well as to test hypotheses regarding the current dominating modes of transmission.

We recognize that incidence estimates are only as valid as the model assumptions are robust. One important limitation of the model is the assumption of constant IRs [9–12]. The degree to which violation of this assumption may have affected model estimates is unpredictable and difficult to assess. We were unable to acquire prevalence data for age intervals of <5 years. Perhaps constancy was absent in some of these age groups, but the natural history of HCV, as well as the strong influence of widespread PAT and iatrogenic exposures, suggest that 5-year-age intervals were reasonable. Since the primary modes of transmission among younger people have yet to be clearly identified, the probability of violating the constant incidence assumption is likely greater, but 5-year intervals seem to be appropriate resolution for examining incidence among younger populations. Furthermore, because HCV has high prevalence in Egypt, the composition of risk groups is likely to change as the population at risk becomes saturated with infection. The steady-state condition assumed by the model may not have been fully met, suggesting that the relation between prevalence, incidence, and duration will only produce rough estimates [12].

The Podgor and Leske-based method can result in negative estimates of the IRs if prevalence at an older age is sharply less than at an earlier age [9,12]. Such estimates obviously are invalid, indicating either: (1) lack of power and/or too much variability among age groups, or (2) the model assumptions do not hold in the age range being examined. Therefore, we were unable to obtain incidence

estimates for age groups >50 years when age-specific prevalence begins to decline. This decline among older age groups supports the hypothesis that the population aged 30–50 years was the most affected by the PAT campaign. It would be valuable to gain prevalence data of the older population in smaller age group intervals and in different geographic locations to examine HCV incidence and PAT trends more closely.

Although the overall prevalence of HCV infection in Egypt is relatively high, the incidence of new infections needed to maintain this prevalence is still low enough that it is difficult to obtain precise incidence estimates. Therefore, results from our modelling approach should not be used to measure changes in IRs over time or differences in IRs between risk groups. Again, this was the principle reason why we chose to estimate incidence from only one study. While estimates from multiple studies could have been calculated, it would have been difficult to tease apart possible violations of assumptions when attempting to compare results or draw broader conclusions. True longitudinal incidence studies are still the best way to identify nuances in incidence trends across age, time and space.

Future HCV-related morbidity and mortality in Egypt

Our natural history model predicted 127 821 deaths from decompensated cirrhosis and 117 556 deaths from hepatocellular carcinoma due to the HCV epidemic over the next 10–20 years. We also calculated that the infected cohort would spend 750 210 years in the diseased state of decompensated cirrhosis, 132 894 years in hepatocellular carcinoma and lose 32.86 million years of life in comparison to an age-sex-matched non-infected cohort. These disturbing projections actually may have underestimated total HCV-related morbidity and mortality for a few reasons. All cases of acute hepatitis were excluded, because Egypt does not have highly accurate data regarding acute infection and its natural history. Thus, we chose to limit our natural history model and projections to those with chronic HCV infection. In addition, the possibility of accelerated progression among older cases or those co-infected with HBV or HIV was not considered, cases that may be more likely to develop hepatic complications [28]. To date there has only been one other model constructed to look at HCV specifically in Egypt, and it involved fitting a model to historic data [29]. Although there was evidence that age- and sex-influenced parameter estimates, confirmatory observational data are not yet presently available for comparison. Consequently, we elected to work with a more conservative model, assuring a baseline, or underestimated, projection of future morbidity and mortality. We also did not evaluate HBV separately. Just as many people were infected with HBV as with HCV during the PAT campaign; however, HBV only caused chronic infections in 5% or less of infected individuals, whereas chronic HCV infection developed in 70–80% [3,6]. This is related to the natural history of HBV, where the probability of developing chronic infection decreases with age [30]. Since most people who received PAT were older than 10–15 years, they were at less risk for developing persistent HBV infection [6]. In addition, the HBV vaccine has been incorporated since 1992, which should lead to a steady decline in the significance of HBV infection, eventually playing only a minor role in the future of liver disease in Egypt.

Our analysis suggested the health burden related to premature mortality or disability from decompensated cirrhosis or hepatocellular carcinoma may be very high. The value of these estimates is that they inform policy makers about the rates at which age-specific groups are becoming infected with HCV and what these estimates will mean in terms of future morbidity and mortality. This information is crucial, because it can lead to conclusions about the level and direction of the HCV epidemic in Egypt that might be less readily apparent from the prevalence data alone. Despite the remarkable decline in new HCV infections since the end of the PAT campaign, mortality related to existing cases will likely continue to increase over the next 10–20 years, similar to the results of Deuffic-Burban *et al.* [29]. Hence, there is an urgent need to address this problem as HCV infection is frequently asymptomatic until cirrhosis develops, when treatment is less effective. More research regarding cost-effectiveness of screening for HCV infection and indications for treatment is needed to help guide public health policy in this area. Continued research on the natural history of HCV and the development of new treatments should remain top priorities not only for Egypt, but for global health as well.

ACKNOWLEDGEMENTS

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APPENDIX 1 LITERATURE INCLUDED IN THE META-ANALYSIS

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