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Epidemiology of hepatitis viruses among hepatocellular carcinoma cases and healthy people in Egypt: A systematic review and meta-analysis

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Liver cancers are strongly linked to hepatitis B virus (HBV) and hepatitis C virus (HCV). Egypt has the highest prevalence of HCV worldwide and has rising rates of hepatocellular carcinoma (HCC). Egypt's unique nature of liver disease presents questions regarding the distribution of HBV and HCV in the etiology of HCC. Accordingly, a systematic search of MEDLINE, ISI Web of Science, ScienceDirect and World Health Organisation databases was undertaken for relevant articles regarding HBV and HCV prevalence in Egypt among healthy populations and HCC cases. We calculated weighted mean prevalences for HBV and HCV among the populations of interest and examined differences in prevalence by descriptive features, including age, year and geographic region. Prevalences for HBV and HCV were 6.7% and 13.9% among healthy populations, and 25.9% and 78.5% among HCC cases. Adults had higher prevalences of both infections (Adult HBV = 8.0%, Child HBV = 1.6%; Adult HCV = 15.7%, Child HCV = 4.0%). Geographically, HBV was higher in the south, whereas HCV was greater in the north (North HBV = 4.6%, South HBV = 11.7%; North HCV = 15.8%, South HCV = 6.7%). Among HCC cases, HBV significantly decreased over time ($p = 0.001$) while HCV did not, suggesting a shift in the relative influences of these viruses in HCC etiology in Egypt. Our results highlight large amounts of heterogeneity among the epidemiological factors associated with liver disease in Egypt and underscore the necessity of an integrated strategy for the successful prevention of viral hepatitis infections and chronic liver disease.

Key words: pooled analysis; liver cancer; infectious diseases; developing countries

Hepatocellular carcinoma (HCC) comprises nearly 6% of all incident cancer cases worldwide, with the overwhelming majority occurring in the developing world.[1] One of the least curable malignancies, HCC is the third most frequent cause of cancer mortality among men worldwide.[1] Chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) have been cited as, by far, the most important etiologic agents.[2] According to the World Health Organisation (WHO), ~350 million people are chronically infected with HBV and 170 million are infected with HCV.[3,4] The relative importance of HBV and HCV as causative agents can vary greatly from region to region and over time.[1,5] Selecting appropriate HCC prevention and control methods, therefore, depends on understanding the dynamics of these agents in a specified geographic region.

Incidence of HCC in Egypt is currently increasing, which may be the result of a shift in the relative importance of HBV and HCV as primary risk factors.[6–8] HCC is the second most frequent cause of cancer incidence and mortality among men in Egypt.[9] Hospital-based studies from Egypt have reported an increase in the relative frequency of all liver-related cancers in Egypt (>95% as HCC), from ~4.0% in 1993 to 7.3% in 2003.[6–8] The Middle East Cancer Consortium recently reported that the incidence rate among males was 7 times greater than the next highest rate (among Israeli Jews) and more than 3 times that reported in the United States Surveillance Epidemiology and End Results summary.[9] To explain this trend it is necessary to understand the dynamics of HBV and HCV in Egypt.

Before implementing the HBV vaccine in the 1980s, chronic infection with HBV was widespread and considered the dominant etiologic factor in HCC development.[10] Childhood HBV immunization in Egypt today is estimated at 95–100%, thus making it likely that HBV-related HCC will steadily decline over the next few decades.[11,12] This transition is not unique to Egypt. Many eastern Mediterranean and Middle Eastern countries are experiencing a decline in HBV due to vaccination campaigns.[13,14] What sets Egypt apart is that this major public health achievement has been eclipsed by the rise of the HCV epidemic, largely attributed to the mass parenteral antischistosomal therapy (PAT) and other iatrogenic exposures.[15–18]

Beginning in the 1950s, the Egyptian Ministry of Health targeted schistosomiasis as its primary health problem, and mounted a massive public health campaign to control it. At the time, the best control method was through injecting individuals with PAT. These campaigns were carried out at the community level as well as in health facilities, where millions of Egyptians were treated with PAT from the 1950s until the 1980s.[18] Needle sterilization was inadequate, and disposable needles were unavailable at that time, leading to widespread transmission of HCV.[16,18] Frank *et al.* (2000) reported the strong relationship between PAT and country-wide prevalence of HCV antibodies for the period 1961–1985. They have cited the PAT campaign as "the world's largest iatrogenic transmission of blood-borne pathogens known to date."[16]

Egypt's high levels of HCV are unique in comparison to nearby countries, even those also heavily burdened by schistosomiasis.[16,19] Though these countries also used PAT to control schistosomiasis, they never mounted any public health campaigns of similar magnitude. Their control efforts were also more focused geographically and less population intensive.[16] This could explain why the burden of HCV in Egypt is so much greater than the surrounding countries with similar schistosomiasis treatments.

Egypt is now plagued by the highest prevalence of HCV in the world, with estimates ranging from 6 to 28% and a reported average of ~13.8%.[20,21] Recent investigations in Egypt have also shown the increasing importance of HCV infection in the etiology of HCC, now estimated to account for 40–50% of cases.[6–8] The future of HCC in Egypt and the magnitude of its socio-economic burden will be a legacy of the country's unique HCV epidemic and the shifting dynamics of HBV and HCV. To date, there has been no systematic review of the literature to synthesize the results of published prevalence studies, including patterns over time. There is, therefore, a need to calculate the fluctuating prevalences of HBV and HCV in Egypt over the past 2 decades among a healthy population-based sample; there is also a need to synthesize data about HCC patients, using appropriate meta-analytic tools. This paper aims to calculate weighted average prevalences of HBV and HCV among 2 groups in Egypt from 1985 to the

Abbreviations: Anti-HCV, hepatitis C virus antibody; HBsAG, hepatitis B virus surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HPW, healthy pregnant women; RBD, replacement blood donors; VBD, voluntary blood donors.

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present: healthy, population-based samples (nonhigh risk) and incident HCC cases.

Material and methods

Literature search methods

MEDLINE, ISI Web of Science, ScienceDirect and WHO regional indexed databases were used to search for articles published from January 1 1980 to October 31 2007, by means of the MeSH terms of: "HCC and Egypt", "HBV and Egypt" and "HCV or hepacvirus and Egypt'. No language limitation was imposed. For HCC studies, the time and place of subject recruitment were cross-checked to avoid inclusion of the same cases in multiple articles. Articles or reports from nonpeer-reviewed sources were not considered for this analysis.

Data analyzed

The key information abstracted from each study included: (*i*) year(s) conducted, to account for the delay between field work and publication; (*ii*) sample size; (*iii*) age range of participants, with $\geq$18 years considered adults; (*iv*) geographic region of the sample (upper or lower Egypt); (*v*) type of residence (urban or rural); (*vi*) prevalence of hepatitis B surface antigen (HBsAg); (*vii*) prevalence of anti-HCV antibodies (anti-HCV); and (*viii*) type of HCV serology test used. We could not examine sex differences in HBV and HCV infection, because too few studies reported virus marker prevalence stratified by participant gender. Similarly, we could not examine HBV and HCV coinfection as it was rarely reported.

Inclusion and exclusion criteria

Healthy population-based studies included the following sample populations: (*i*) voluntary blood donors (VBD); (*ii*) replacement blood donors (RBD) typically from friends or blood relations; (*iii*) healthy antenatal women; and (*iv*) community studies. We excluded studies from the following special groups who were assumed to be at special high risk: patients from sexually-transmitted-disease clinics, thalassemia clinics, hospitalised patients, professional or paid blood donors, sex workers, drug abusers, dialysis patients and health care workers. Healthy population-based studies with fewer than 100 participants were excluded from this analysis.

HCC studies were limited to those examining incident cases to avoid temporal ambiguity and the possibility that virus infection may have occurred subsequent to the cancer diagnosis. HCC studies with fewer than 25 participants were excluded from this analysis.

Eligible studies had to report prevalence of HBsAg and/or anti-HCV. Studies were excluded if they failed to indicate the type of test used to assess infection status and if the sensitivity and specificity of the test was unknown. Information regarding HBV infection and immunity status can be obtained from 4 common seromarkers: HBsAg, anti-HBs, total hepatitis B core antibody (anti-HBc) and IgM antibody to hepatitis B core antigen (IgM anti-HBc). Of these markers, only HBsAg can identify the current infection. A positive result indicates either active or chronic infection. Antibody markers cannot distinguish between naturally-acquired immunity and vaccine-related immunity.[22] Since we wanted to measure the prevalence of naturally acquired infection, HBsAg was the seromarker of interest. In addition, these tests are inexpensive, simple to conduct, reliable and have been available for a long time, allowing them to be fairly standard even in low-resource settings.[22]

HCV infection status can be determined in 2 primary ways: enzyme immunoassay (EIA) or polymerase chain reaction (PCR). EIA techniques indicate the presence of antibody (anti-HCV) while PCR can serve to confirm infection as well as measure viral load. Both methods indicate ongoing infection and do not correlate well with resolved infection. As with HBsAg, anti-HCV does not distinguish between acute and chronic infection.[23] While PCR techniques tend to be more accurate, they are far more expensive and, thus, infeasible for low-resource settings or areas with higher prevalence. With a sensitivity greater than 95% and the availability of standardized test kits, the WHO recommends EIA as the primary screening tool and suggests PCR be used for clinical and case management purposes.[23] For these reasons, it is rare to find PCR tests reported in the literature from lower-resource settings such as Egypt and we believe the results of EIA are sufficiently consistent and reliable to be used in this analysis. Though some studies did report both anti-HCV and PCR results, we only examined anti-HCV to limit bias due to varying test sensitivity and specificity.

In addition, studies known or likely to have used first-generation ELISA for measuring anti-HCV were not included in this meta-analysis due to known problems of sensitivity and specificity of those assays.[24] To date, there have been 3 generations of anti-HCV EIAs, with the first developed in 1990. It suffered from poor sensitivity and could not detect antibody prior to 4–6 months following initial infection. These tests also lacked sufficient specificity, resulting in numerous false positive results. Second and third generation tests have dramatically improved sensitivity (>95%) and narrowed the window period between infection and anti-HCV detection.[23] Consequently, this analysis only considered reports that used second or third generation anti-HCV EIAs, thereby excluding 3 studies.

We also applied specific definitions when classifying Lower and Upper Egypt as well as urban and rural settings.[25] Lower and Upper Egypt are broad geographic designations that respectively refer to the north and south regions of Egypt. They are termed according to the flow of the Nile, which runs south to north. Lower Egypt is so termed, because it lies further downstream. Studies have suggested that HCV prevalence differs between Lower Egypt in the north and Upper Egypt in the south.[6,7] Thus, we compared studies of these 2 regions which comprised the vast majority of published reports.

The Egyptian government classifies "governorates" (*muhafazat*) as either fully urban or joint urban and rural.[25] The official distinction between urban and rural is reflected in the lower tiers. Fully urban governorates have no districts (*markazes*) which are defined as a conglomeration of villages around a capital city. In joint urban and rural governorates, therefore, urban locations are comprised of each district's capital city. All other locations in that governorate are considered rural. Some urban governorates consist of just 1 city (*e.g.* Cairo which has 23 urban neighborhoods). HCV prevalence differences between urban and rural populations have been suggested, so we systematically explored this hypothesis using strict and consistent definitions.[8,15–18,26]

Statistical power

Two types of statistical power issues exist: small participant sample size in individual studies and small sample size of studies, particularly when stratified by subfactors of analysis (*e.g.* geographic region, age group, etc). Pooling 30 studies with sample sizes of 50, for example, may not be as reliable as pooling 5 studies of 300 participants. Nevertheless, it is difficult to compare multiple studies of a particular geographic region to a single study in a different region, regardless of sample size. Our sample size criteria are somewhat arbitrary, but we did base our decision on what is known about the difference in viral prevalence among healthy population samples *vs.* HCC case samples in Egypt. Since little information is available on power calculations for these biomarkers in Egypt, we took a more qualitative approach. Egypt experiences a higher burden of HBV and HCV in its apparently healthy population as compared to other countries, so we believe a minimum sample size of 100 is adequate to detect statistical differences between groups, provided the sample is a genuine representation of the entire population of interest. Sample sizes of HCC studies tend to be small because of the difficulty in obtaining participants.

TABLE I – SUMMARY OF DATA ABSTRACTED FROM HEALTHY POPULATION LITERATURE

Biomarker	Author [citation]	Study period	Population	Region	Residence	Age	*n*	Prevalence (%)
HBsAg	Sherif *et al*. [28]	1983	Community	Lower	Urban and Rural	18+ yr	1,064	11.7
	Sherif *et al*. [28]	1983	Community	Lower	Urban and Rural	18+ yr	802	8.0
	Gumie *et al*. [29]	1988–1990	VBD	Lower	Urban and Rural	18+ yr	1,715	2.5
	El-Sherbini *et al*. [30]	1991	School children	Lower	Urban and Rural	<18 yr	198	1.5
	El-Hawey *et al*. [31]	1991–1992	Community	Lower	Rural	18+ yr	300	15.7
	Arthur *et al*. [32]	1993	VBD	Upper and Lower	Urban and Rural	18+ yr	1,030	12.7
	Mabrouk *et al*. [33]	1993	Army recruits (male)	Lower	Urban and Rural	18+ yr	297	1.7
	Darwish *et al*. [34]	1993	VBD	Lower	Urban and Rural	18+ yr	163	3.2
	Darwish *et al*. [35]	1995	Community	Lower	Urban and Rural	18+ yr	796	8.8
	El-Sherbini *et al*. [30]	1995	School children	Lower	Rural	<18 yr	300	0.7
	Reda *et al*. [36]	1997	Community	Lower	Urban and Rural	<18 yr	500	2.2
	El-Sherbini *et al*. [30]	2002	School children	Upper	Urban	<18 yr	470	1.5
Anti-HCV	El-Sherbini *et al*. [37]	1991	School children	Lower	Rural	<18 yr	138	15.9
	El-Sherbini *et al*. [37]	1991	School children	Lower	Urban	<18 yr	130	6.2
	El-Sherbini *et al*. [37]	2002	School children	Lower	Urban	<18 yr	470	2.1
	Fathalla *et al*. [38]	1991–1992	VBD	Upper and Lower	Urban and Rural	18+ yr	248	18.2
	Arthur *et al*. [32]	1993	VBD	Upper and Lower	Urban and Rural	18+ yr	2,644	24.8
	Darwish *et al*. [34]	1993	VBD	Lower	Rural	18+ yr	163	22.0
	El-Sherbini *et al*. [37]	1994	School children	Lower	Rural	<18 yr	294	2.0
	Kumar *et al*. [39]	1994–1996	HPW	Lower	Urban and Rural	18+ yr	499	15.0
	Darwish *et al*. [35]	1995	Community	Lower	Urban and Rural	18+ yr	796	40.3
	Kassem *et al*. [40]	1996	HPW	Lower	Urban and Rural	18+ yr	100	19.0
	Mohamed *et al*. [41]	1997	Community	Lower	Rural	<18 yr	1,823	8.2
	Mohamed *et al*. [41]	1997	Community	Upper	Rural	<18 yr	2,808	2.5
	Stoszek *et al*. [42]	1997–2003	HPW	Lower	Urban and Rural	18+ yr	2,587	15.8
	Abdel Aziz *et al*. [43]	1999	Community	Lower	Rural	18+ yr	3,999	24.3
	Nafeh *et al*. [44]	1999	Community	Upper	Rural	18+ yr	6,031	8.7
	Tanaka *et al*. [45]	1999	VBD	Upper and Lower	Urban and Rural	18+ yr	3,608	8.8
	Rizk *et al*. [46]	2000–2002	HPW	Lower	Urban and Rural	18+ yr	696	15.8
	Bakr *et al*. [47]	2002	Community	Lower	Rural	18+ yr	4,720	19.3
	Mohamed *et al*. [48]	2002	Community	Lower	Rural	18+ yr	2,425	18.5
	Arafa *et al*. [20]	2002–2003	Community	Lower	Rural	18+ yr	4,020	11.8
	Raouf *et al*. [49]	2002–2003	HPW	Lower	Urban and Rural	18+ yr	1,832	10.1
	El-Sadawy *et al*. [50]	2003	Community	Lower	Rural	18+ yr	842	27.4
	El-Sadawy *et al*. [50]	2003	Community	Lower	Urban	18+ yr	580	23.4
	El-Raziky *et al*. [51]	2004	Community	Lower	Urban and Rural	<18 yr	1,042	1.4

VBD, voluntary blood donors; HPW, healthy pregnant women.
Total *n* for HBsAg studies = 7,597.
Total *n* for anti-HCV studies = 42,457.

Since an overwhelming majority of HCC cases in Egypt, test positive for HBV and/or HCV, we believe sample sizes of 25 and greater will provide sufficient statistical power.[6,9]

Meta-analysis

Data were analyzed according to 3 different categories: HBV prevalence among healthy population-based samples, HCV prevalence among healthy population-based samples and HBV and HCV prevalence among incident HCC cases. Summary prevalence measures were calculated as averages weighted by individual study sample size, using a standard method.[26] These summary measures were used to compare differences between sub-groups in aggregate, as well as over time. Chi-square tests ($\alpha = 0.05$) were performed to determine significant differences in prevalence with respect to age category (child *vs.* adult), geographic location (Upper *vs.* Lower Egypt), type of residence (urban *vs.* rural) and study period (time; treated as a continuous variable).

Sensitivity analysis did not reveal any outlier or influential prevalence estimates among the healthy population studies. One study was found to be influential in lowering the estimate of anti-HCV prevalence among HCC cases (Attia *et al*., 1996).[27] Because this study measured only anti-HCV and not HBsAg, it was controlled for when we repeated our calculations to include only those studies that measured both HBsAg and anti-HCV. We present results from both calculations here.

All manipulations and analyses were performed using SAS v 9.1.3 (SAS Institute, Cary, NC) and MetaWin v 2.0 (Sinauer Associates, Sunderland, MA).

Results

Literature search results

The initial search generated >1,500 potential articles which was refined to 200 relevant articles from MEDLINE ($n = 107$), WHO regional indexed databases (57), ISI Web of Science (34) and ScienceDirect (2). A hand search of the reference lists of selected articles identified a few additional relevant studies. Final results from our search yielded a total of 39 unique peer-reviewed studies meeting our inclusion/exclusion criteria. Several studies measured both HBsAg and anti-HCV and some of them also involved more than one study site, providing prevalence measures for multiple population samples. Of these studies, 25 studied healthy population-based samples and 14 were specific to HCC cases. The healthy population-based studies included 12 with HBsAg measurements and a total sample size of 7,597 and 24 with anti-HCV measurements and a total sample size of 42,457. The 14 HCC case investigations with HBsAg and/or anti-HCV information had a total case population of 3,275. The time periods of data varied: 1983–2002 for HBV among healthy population-based samples, 1991–2004 for HCV studies among healthy population-based samples and 1985–2005 for HCC studies. Data abstracted from the studies are presented in Tables I, II. Results from weighted means and chi-square tests for all categories among HBV, HCV and HCC are presented in Table III.

HBsAg among healthy population-based samples

Overall, the prevalence of HBsAg among healthy population-based samples was 6.7% (±1.4%), with no significant variation

TABLE II – SUMMARY OF DATA ABSTRACTED FROM HCC CASE LITERATURE

Author	Study period	Patient source	Study *n*	HBsAg+ (%)	Anti-HCV+ (%)
Ahmed *et al*. [52]	1985	Tropical Medicine Department, Cairo University	25	28.0	–
El-Soudani *et al*. [53]	1989–1992	Al-Azhar University	38	73.7	–
El-Sherif *et al*. [54]	1991–1992	Mansoura University	30	30.0	70.0
El-Zayadi *et al*. [6]	1992–1995	Cairo Liver Center	321	38.6	85.7
Abdel-Wahab *et al*. [55]	1992–2005	Medical Research Institute, Alexandria University	1,012	–	79.6
Abdel-Wahab *et al*. [56]	1993	National Cancer Institute, Cairo	60	33.3	–
Angelico *et al*. [57]	1993–1995	National Cancer Institute, Cairo	135	15.6	67.4
Attia *et al*. [27]	1995	Ain Shams University Hospital	429	–	53.4
Hassan *et al*. [7]	1995–1996	National Cancer Institute, Cairo	33	15.2	75.8
Mabrouk *et al*. [58]	1995–1996	Ain Shams University Hospital	34	20.6	94.1
Yates *et al*. [12]	1997–1998	National Cancer Institute, Cairo	131	61.8	73.3
El-Zayadi *et al*. [59]	1998–2002	Cairo Liver Center	750	20.5	87.9
El-Kafrawy *et al*. [60]	1999–2002	Ain Shams University Hospital and NCI, Cairo	41	2.4	87.8
Ezzat *et al*. [61]	2003–2004	National Cancer Institute, Cairo	236	7.6	86.4

Total *n* for all studies = 3,275.
All studies had a mean age between 45 and 60 yrs.

TABLE III – PREVALENCE ESTIMATES AND CHI-SQUARE RESULTS FOR ALL CATEGORIES OF ANALYSIS AND COMPARISON GROUPS

Population of analysis	Category of analysis	Comparison group	Prevalence (%)	# Studies	Total *n*	χ^2 *p*-value
HBsAg–healthy population	Age	Adult	8.0	8	6,129	<0.0001
		Child	1.6	4	1,468	
	Time (total)	1983–1992	6.9	5	4,079	0.5900
		1993–1995	6.5	7	3,518	
	Time (adult)	1983–1992	7.1	4	3,881	0.0027
		1993–1995	9.3	4	2,248	
	Time (child)	1991–1993	1.5	1	198	0.8478
		1994–1997	1.6	2	800	
		1998–2002	1.5	1	470	
	Region (total)	Lower Egypt	4.6	10	5,503	<0.0001
		Upper Egypt	11.7	1	1,064	
Anti-HCV–healthy population	Age	Adult	15.7	17	35,752	<0.0001
		Child	4.0	7	6,705	
	Time (total)	1990–1994	21.79	6	3,579	<0.0001
		1995–1999	12.45	8	19,664	
		2000–2004	13.54	9	16,627	
	Time (adult)	1990–1994	24.7	3	3,017	<0.0001
		1995–1999	14.8	6	15,033	
		2000–2004	14.8	7	15,115	
	Time (child)	1990–1994	6.4	3	562	<0.0001
		1995–1999	4.8	2	4,631	
		2000–2004	1.0	2	1,512	
	Region (total)	Lower Egypt	15.8	19	27,118	<0.0001
		Upper Egypt	6.7	2	8,839	
	Region (adult)	Lower Egypt	17.6	16	23,221	<0.0001
		Upper Egypt	8.7	1	6,031	
	Region (child)	Lower Egypt	5.1	7	3,897	<0.0001
		Upper Egypt	2.5	1	2,808	
	Residence (total)	Rural	13.4	10	27,100	<0.0001
		Urban	5.5	3	1,180	
	Residence (adult)	Rural	15.4	9	22,037	<0.0001
		Urban	8.1	1	580	
	Residence (child)	Rural	4.9	1	5,063	0.0003
		Urban	3.0	2	600	
HCC Cases (All studies)	Infection prevalence	HBV	25.9	12	1,834	<0.0001
		HCV	78.5	10	3,140	
	Infection prevalence	HBV (1985–1996)	32.7	8	676	<0.0001
		HCV (1991–1996)	68.5	6	982	
	Infection prevalence	HBV (1997–2004)	21.9	4	1,158	<0.0001
		HCV (1997–2004)	85.9	4	1,158	
	HBV prevalence	1985–1996	32.7	8	676	<0.0001
		1997–2004	21.9	4	1,158	
	HCV prevalence	1991–1996	68.5	6	982	<0.0001
		1997–2004	85.9	4	1,158	
HCC Cases (Only studies measuring both HBsAg and anti-HCV)	Infection prevalence (total)	HBV	24.5	9	1,711	<0.0001
		HCV	84.1	9	1,711	
	Infection prevalence (1991–1996)	HBV	30.0	5	553	<0.0001
		HCV	80.3	5	553	
	Infection prevalence (1997–2004)	HBV	21.9	4	1,158	<0.0001
		HCV	85.9	4	1,158	
	HBV prevalence	1991–1996	30.0	5	553	0.0010
		1997–2004	21.9	4	1,158	
	HCV prevalence	1991–1996	80.3	5	553	0.2015
		1997–2004	85.9	4	1,158	

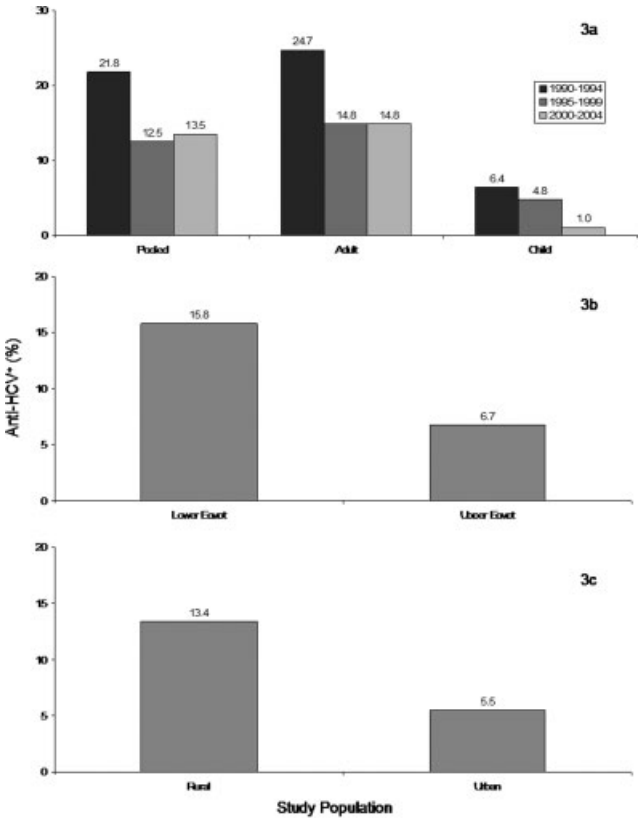

FIGURE 1 – Prevalence of anti-HCV+ individuals. The top graph shows prevalence over 3 time periods: 1990–1994, 1995–1999 and 2000–2004. The difference observed across time period was highly significant (total, adult and child; $p < 0.0001$). The middle graph illustrates prevalence by geographic region ($p < 0.0001$). The bottom graph shows prevalence by type of residence ($p < 0.0001$).

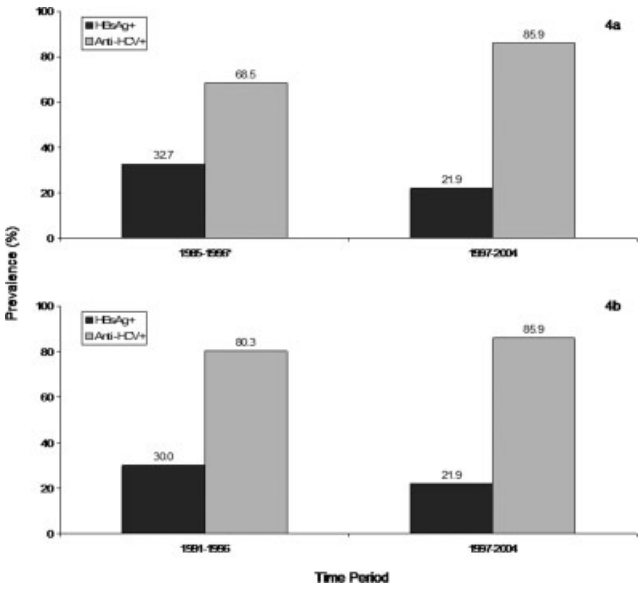

FIGURE 2 – Prevalence of HBsAg and anti-HCV+ among HCC cases. The top graph shows prevalence over the 2 time periods: 1985–1996 and 1997–2004. Differences across biomarkers as well as within biomarkers over time were significant ($p < 0.0001$). The bottom graph presents prevalence over the 2 time periods: 1991–1996 and 1997–2004, using only studies that reported both HBsAg and anti-HCV measurements. Differences between HBsAg and anti-HCV were significant ($p < 0.0001$), as were differences within HBsAg prevalence over time ($p = 0.001$) but time differences within anti-HCV were not significant ($p = 0.2051$).

over time ($p = 0.59$) (Table III). When these studies were separated according to age, the pattern was similar, however, prevalence was significantly higher among adults than children ($p < 0.0001$). Adults averaged a prevalence of 8.0% (±1.7%), with children averaging at 1.6% (±0.3%), likely a function of the introduction of the HBV vaccine.

Eleven of 12 healthy HBsAg studies provided information regarding individuals from Lower Egypt with an average prevalence of 4.6% (±1.3%), lower than that of the Upper Egypt study 11.7% ($p < 0.0001$). The one study from Upper Egypt may not be representative, but it was a community-based sample of 1,064 individuals.

Anti-HCV among healthy population-based samples

Table III also presents the major findings from examining the prevalence of anti-HCV among healthy population-based samples. Overall, from 1990 to 2004 the prevalence was 13.9% (±1.6%), also significantly higher among adults (15.7% ± 1.8%) *versus* children (4.0% ± 2.1%; $p < 0.0001$). Unlike findings with HBsAg, however, anti-HCV prevalence seemed to vary over time, both in summary and by age group (Fig. 1; Table III). Studies from 1990 to 1994 showed a higher prevalence of 21.8 (±3.3%) when compared to the time periods 1995–1999 (12.5% ± 3.4%) and 2000–2004 (13.5% ± 2.0%), which were not statistically different from one another. This trend continued for adults ($p < 0.0001$), but child studies suggested a continuing decline in prevalence ($p < 0.0001$; Fig. 1).

Analysis of anti-HCV by geographic region found the reverse trend from what was observed with HBsAg (Fig. 1). Of the 24 total studies, 19 had specific information on Lower Egypt and 2 had specific measurements for Upper Egypt. Studies from Lower Egypt showed a significantly higher prevalence (15.8% ± 1.8%) than those from Upper Egypt (6.7% ± 2.9%) ($p < 0.0001$), a pattern that remained stratifying by age group (Table III).

We compared studies of urban ($n = 3$) and rural ($n = 10$) populations. As the literature has suggested, there was a significantly higher prevalence of anti-HCV among rural populations (13.4% ± 2.3%) compared to urban populations (5.5% ± 2.0%) ($p < 0.0001$). Again, this trend remained highly significant after stratifying by age group (Table III).

HBsAg and anti-HCV among HCC cases

Finally, Table III presents findings on the prevalence of HBsAg and anti-HCV among HCC cases. There were 12 studies with HBsAg data covering the time period 1985–2004 and 11 studies with anti-HCV measurements spanning 1991–2004. The overall prevalence of HBsAg was 25.9% (±4.7%) and that of anti-HCV was 78.5% (±3.6%), a statistically significant difference ($p < 0.0001$). Both markers showed highly significant changes over time, with HBsAg decreasing (1985–1996: 32.7% ± 5.2%; 1997–2004: 21.9% ± 8.9%; $p < 0.0001$) and anti-HCV increasing (1991–1996: 68.5% ± 6.6%; 1997–2004: 85.9% ± 2.6%; $p < 0.0001$) over time (Fig. 2).

Of the HCC studies included, 9 ($n = 1711$) reported both HBsAg and anti-HCV measurements. The above analysis for these 9 studies was repeated to reduce the possibility of bias due to early generation ELISA tests, but results were similar. The overall prevalence of HBsAg was 24.5% (±5.1%) and that of anti-HCV was 84.1% (±2.4%). The decrease in HBsAg remained significant (1991–1996: 30.0% ± 5.3%; 1997–2004: 21.9% ± 8.9%; $p = 0.001$). A slight increase in anti-HCV prevalence was observed for the revised group of studies, but it was no longer significant

(1991–1996: 80.3% ± 4.3%; 1997–2004: 85.9% ± 2.6%; $p = 0.2015$) (Fig. 2).

Discussion

This is the first systematic review and meta-analysis of hepatitis B and C virus prevalence in Egypt and provides insights for understanding the past and future dynamics of liver disease there. For HBV and HCV in healthy population-based samples, adults had a significantly higher prevalence than children, supporting an independent age cohort effect for both viruses. For HBV, it seems likely that the cohort effect would be related to the introduction of the hepatitis B vaccine in 1992, which was incorporated into the expanded programme on immunization and is only given to children, leaving adults unvaccinated at the time of program implementation. This explains the discrepancy in prevalence between adults and children in our analysis. It should be noted that childhood HBV studies do not begin appearing until the vaccine program had been introduced, as they were designed to evaluate the vaccine's success. Therefore, we were not able to compare childhood HBV prevalence between unvaccinated and vaccinated groups, nor were we able to find reports of adult and child prevalence in the same individual study. Based on the timing of the studies and the large difference in prevalence between adults and children, however, it seems logical to conclude that the vaccine is responsible for the consistently low levels of HBV in children and higher prevalence among the unvaccinated adults.

The cohort effect seen in HCV is consistent with other studies that report higher prevalences in age groups older than 30 yrs.[8,15–17] These studies were focused on identifying risk factors for HCV infection and often did not present prevalence results conducive for use in the meta-analysis, which is why they were not included. The age cohort observation is likely related to the early association between the parenteral antischistosomiasis therapy (PAT) campaign and HCV transmission. Oral therapies for schistosomiasis were gradually adopted in the 1980's, dramatically reducing transmission.[16,62] It is still unclear, however, what the rate of HCV transmission is presently, in the absence of the original primary route. Since several of the childhood HCV studies were late enough that none of the children would have been exposed to the PAT campaign, it does appear that HCV has continued to be transmitted. It will be important to understand the emerging routes and rates of transmission to effectively control the burden of liver disease in Egypt.

Our analysis confirmed reports of large scale geographic heterogeneity in HCV prevalence.[6,7] We found prevalence to be significantly higher in Lower Egypt as opposed to Upper Egypt, which in turn supports the hypothesis of PAT as the dominant force driving the HCV epidemic. Individuals living in Lower Egypt experienced a greater burden of schistosomiasis and therefore a greater level of exposure to PAT.[6,7] This is consistent with the only study we found directly comparing HCV prevalence in a Lower Egypt village and an Upper Egypt village (both rural). Mohamed *et al.* (2006) conducted a childhood study in 1997, reporting a prevalence of 8.2% in Lower Egypt and 2.5% in Upper Egypt.[48] This is a slightly larger disparity than what the pooled analysis revealed (Lower Egypt: 5.1%; Upper Egypt: 2.5%), but this does not necessarily indicate inconsistency. Our results are unadjusted for year to prevent over-stratification, whereas these findings were from the same time period. Since we observed decreasing prevalence among children over time and our analysis included data through 2002, we would expect the pooled result to be lower. We would also expect greater variance in our estimates since we are pooling studies from multiple, different study sites.

This is in contrast to what we saw with HBV, which seemed to be higher in Upper Egypt *versus* Lower Egypt. Unfortunately, the number studies of HBV prevalence in Upper Egypt was inadequate and we were unable to find any studies specifically comparing HBV in Upper and Lower Egypt, so it is best not to draw too many conclusions from that analysis.

We were also able to examine the relationship of HCV with urban and rural populations, with results supporting the hypothesis that HCV prevalence is higher among rural residents than urban residents.[8,15,63] Sherbini *et al.* (2006) examined HCV prevalence among children in an urban setting in 1991 and 2002 and in a rural setting in 1991 and 1994. The results indicated a higher HCV prevalence in the rural region both times. In 1991, urban children had a HCV prevalence of 6.2% while rural children experienced a prevalence of 15.9%.[30] Again, in 1994, Sherbini *et al.* reported a prevalence of 5.8% in the rural setting and 2.1% in the 2002 urban study.[30] This trend is consistent with our results. We found a large disparity among adults, with a prevalence of 15.4% and urban prevalence of 8.1%. This corresponds with the 1991 studies and that age cohort would all be adults at the time of more recent studies. The difference in rural and urban HCV prevalence was less pronounced in the pooled estimates for children (rural: 4.9%; urban: 3.0%). Again, this is logical considering the documented decrease in HCV prevalence over time among children. Sherbini *et al.* unfortunately do not have rural estimates more recent than 1994, making a direct comparison difficult. Nevertheless, the trend observed in the Sherbini *et al.* study is supportive of our pooled estimates. This finding is also in line with the PAT hypothesis; that rural residents would have a greater burden of schistosomiasis and therefore greater exposure to PAT.[15–17,63]

We were only able to find one childhood study that directly examined HBV in urban and rural settings. Sherbini *et al.* (2007) compared measurements from a 1995 study in a rural village with a 2002 study in an urban setting (both in Lower Egypt). They found a prevalence of 1.9% in the rural village and 1.1% in the urban city, which were not statistically different from one another.[37] Because this was the only study to explicitly identify separate urban and rural prevalences, we did not include it in the meta-analysis. The finding is not surprising, however, since both studies were conducted after the establishment of the HBV vaccination program. The time difference between the 2 studies (rural: 1994; urban: 2002) could explain why the rural prevalence is slightly higher. The vaccine program had only been in place for a couple of years, so some unvaccinated children may have been included.

Since most of the HCC studies were hospital-based, it is difficult to speculate on future effects even though more HCC cases would be expected in rural regions. This is contrary to a recent population-based HCC study from Lower Egypt that found cases to be nearly twice as likely to come from urban *versus* rural areas.[64] Due to the significant lag time between viral infection and development of HCC, it is possible that Egypt is witnessing the end of a cohort of higher urban exposure that will soon transition to a population dominated by rural exposure.

It was illuminating to examine the trends in HBV and HCV prevalence over the past 20 years. We did see a slight increase over time in HBV prevalence among adults from 7.1 to 9.3%. It is likely that this may also be a product of the PAT campaign. The same number of people were infected with HBV and HCV during the PAT campaign; however, HBV only caused chronic infections in ~5% of infected individuals, whereas chronic HCV infection developed in 70 to 80%.[16,18] This can be explained by the natural history of HBV, where the probability of developing chronic infection decreases with age.[10] Since most individuals receiving PAT were 10–15 years or older, they were at less risk for developing persistent HBV infection.[18] This could explain why we saw an increase in HBV prevalence in the healthy population without a similar increase among HCC cases. Among children, however, HBV prevalence was low, probably due to the implementation of earlier control measures followed by the vaccine. Infection levels in children suggest that this infection may soon be an insignificant element of the liver disease burden in Egypt.

Unlike HBV, prevalence of HCV showed greater variance over time. Among both children and adults there was a general decline

in prevalence over time, with adults stabilizing at just below 15% and children continuing to drop to nearly 1% by the period 2000–2004. Detailed risk factor data are needed to further characterize if time and space interactions are occurring and distinguish between the effects of population migration, changing risk factor patterns, etc. It would also be valuable to match these prevalence figures with incidence studies to reconstruct the different epidemic curves, shedding light on viral dynamics and guiding predictions about future trends in infection.

A summary understanding of the status of HBV and HCV prevalence in healthy population-based samples should be complimented by viral dynamics among HCC cases. Frequently the burden of HBV and HCV cannot easily be quantified apart from its chronic sequelae. By understanding the degree to which these viruses contribute to HCC, it is possible to see the impact they have on overall population health. The overall prevalence of HBV among HCC cases was nearly 25%, with HCV infection prevalence as high as 84%. Some differences were noted over time although not statistically significant, possibly a result of low power. It seemed that HBV infection declined from a prevalence of 30% between 1991 and 1996 to 22% between 1997 and 2004. Conversely, HCV infection among HCC cases may have increased slightly over this same time period from 80 to 86%. This is consistent with the impact of the 2 different cohort effects. Current cancer cases represent individuals being exposed to these viruses 20–30 years prior. These cases may represent the individuals at the end of the pre-HBV vaccine period and the beginning of the PAT campaign. Based on anticipated demographic changes, it seems likely that prevalence of HBV will continue to decline and HCV will continue to increase among HCC cases for the next few decades. Indeed, results from mathematical models designed to predict the future burden of HCV in Egypt are consistent with this hypothesis.[63] What happens after that will depend largely on the new HCV incidence patterns in the absence of the PAT campaign.

Despite our extensive literature search, the specific search terms used may not have captured all quality papers published in peer-reviewed indexed journals. For this reason, we supplemented our electronic search by a hand search of references from selected articles, but there is always the possibility that some studies were missed. We attempted to gain representative samples of the Egyptian healthy population by accepting community-based samples, but also included some large scale convenience samples such as healthy pregnant women attending clinics and VBD. The inclusion of VBD in systematic reviews has been questioned in a study at Vellore, India where the HBV carrier rate was 0.7%, considered artificially low because donors are a self-selected group and HBV-positive people do not repeat donations.[65] However, another analysis of different population groups tested in Delhi, found voluntary donors, replacement donors and ante-natal mothers all had prevalences close to the overall mean.[66] The extent to which the HCC cases we reported upon are representative is also unclear, since in most cases only hospital-based studies were available. We did focus on cancer studies from the larger, nationally recognized cancer centers, which serve as diagnostic and treatment facilities for the overwhelming majority of cancer cases throughout Egypt.

Only a large, national epidemiological study can provide a definitive answer regarding the overall prevalence of hepatitis B and C viruses in Egypt. Lacking such a national sample survey, our systematic review and meta-analysis of high quality studies previously conducted provides a useful compromise. These findings highlight the significance of continuing prevention of HBV through vaccination campaigns as well as the development of an integrated strategy for the prevention of HCV infection that should include screening of blood donations, safe injection practices and avoidance of unnecessary injections. Controlling transmission of these 2 viruses should effectively reduce the burden of HCC in Egypt.

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