RESEARCH ARTICLE

Burden of Virus-associated Liver Cancer in the Arab World, 1990-2010

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Abstract

Hepatocellular carcinoma (HCC) is amongst the top three cancer causes of death worldwide with hepatitis B and C viruses (HBV/HCV) as the main etiological agents. An up-to-date descriptive epidemiology of the burden of HBV/HCV-associated HCC in the Arab world is lacking. We therefore determined the burden of HBV/HCV-associated HCC deaths in the Arab world using the Global Burden of Disease (GBD) 2010 dataset. GBD 2010 provides, for the first time, deaths specifically attributable to viral-associated HCC. We analyzed the data for the 22 Arab countries by age, sex and economic status from 1990 to 2010 and compared the findings to global trends. Our analysis revealed that in 2010, an estimated 752,101 deaths occurred from HCC worldwide. Of these 537,093 (71%) were from HBV/HCV-associated HCC. In the Arab world, 17,638 deaths occurred from HCC of which 13,558 (77%) were HBV/HCV-linked. From 1990 to 2010, the burden of HBV and HCV-associated HCC deaths in the Arab world increased by 137% and 216% respectively, compared to global increases of 62% and 73%. Age-standardized death rates also increased in most of the Arab countries, with the highest rates noted in Mauritania and Egypt. Male gender and low economic status correlated with higher rates. These findings indicate that the burden of HBV/HCV-associated HCC in the Arab world is rising at a much faster rate than rest of the world and urgent public health measures are necessary to abate this trend and diminish the impact on already stretched regional healthcare systems.

Keywords: Hepatitis B virus - hepatitis C virus - hepatocellular cancer - Arabs - cancer risk factors

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Introduction

Hepatocellular carcinoma (HCC), the main form of primary liver cancer, is one of the most common cancer causes of death in many countries (Jemal et al., 2012; Yeo et al., 2013). HCC is an aggressive malignancy with over 50% of the cases dying within the first year of diagnosis (Altekruse et al., 2009). There is significant gender and regional variation. The highest incidence rates are found in East Asia and Sub-Saharan and Western Africa (El-Serag and Rudolph, 2007; Liu et al., 2014) with male:female ratio of more than 2:1 (Jemal et al., 2011). The differing geographical incidence rates of HCC correlate with seropositivity rates for hepatitis B (HBV) and hepatitis C (HCV) virus infection (Colombo et al., 1989; Kew et al., 1990). It is now well established that three risk factors, namely chronic infection with HBV, HCV and alcohol independently and in combination predominantly contribute to the development of HCC (Donato et al., 2002; Morgan et al., 2004).

Globally, viral-associated HCC is by far the most common type. Although both HBV and HCV have tropism for hepatocytes, the two viruses are very different. HBV is a small (3.2kb) DNA virus belonging to the hepadnaviridae family and is transmitted to humans via exposure to infected blood or body fluids (Seeger et al., 2013). The most common routes of transmission are perinatal, sexual intercourse and through sharing needles amongst intravenous drug users. It is estimated that over 2 billion people worldwide have been infected with HBV and over 360 million have chronic infection (Shepard et al., 2006). Chronic infection in turn is strongly associated with the development of HCC. However, the details of the molecular steps involved in the development of HCC remains poorly understood. Hepatitis C on the other is an enveloped positive-strand RNA virus belonging to the flaviviridae family (Ray et al., 2013). The main modes of transmission of HCV are the same as those for HBV. Moreover, the target cells of HCV are also hepatocytes, infection of which is mediated by binding to one of several receptors, including CD81 (Pileri et al., 1998) and occludin (Ploss et al., 2009).

In this study we assess the burden of HCC in the 22 Arab countries that form the Arab world. We provide the most up-to-date and detailed descriptive epidemiology of HBV and HCV-associated HCC deaths in the Arab world using the Global Burden of Disease, Injuries and Risk Factors Study 2010 (GBD 2010) dataset (Lozano et al., 2012; Murray et al., 2012a). GBD 2010 provides, for the first time an opportunity to specifically address the

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Table 1. Deaths from Liver Cancer by Risk Factor: Comparison of the Arab World With Global Trends, 2010

Risk factor	Global Deaths					Deaths in the Arab World				
	Deaths (male)	Deaths (female)	Deaths (both)	% of total	% Males affected	Deaths (male)	Deaths (female)	Deaths (both)	% of total	% Males affected
HBV	257,235	84,145	341,380	45.4	75.4	4,409	2,038	6,447	36.6	68.4
HCV	118,606	77,107	195,713	26	60.6	4,311	2,800	7,111	40.3	60.6
Alcohol	101,042	47,919	148,962	19.8	67.8	1,471	867	2,338	13.3	62.9
Others	43,335	22,711	66,046	8.8	65.6	982	760	1,742	9.9	56.4
Total	520,218	231,882	752,101	100	69.2	11,173	6,464	17,638	100	63.3

*Legend: Absolute number of deaths from liver cancer worldwide and in the Arab world, by risk factor and gender for the year 2010. The percentage of liver cancer deaths associated with different risk factors is given, as is the percentage of males that are affected

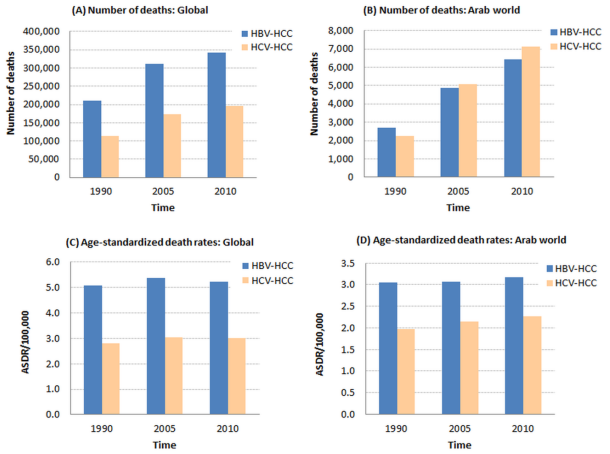

Figure 1. Burden of HBV and HCV-associated Hepatocellular Carcinoma, 1990-2010, Globally and in the Arab World

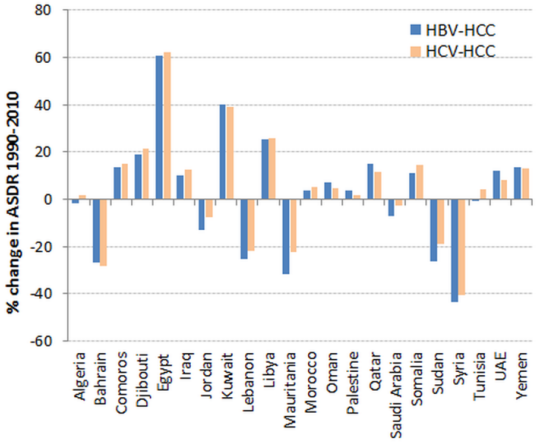

Figure 2. Percentage Change in Age-standardized Death Rates for HBV and HCV-associated Hepatocellular Carcinoma in the Arab World 1990-2010

burden of deaths attributable to HBV and HCV-associated HCC in the Arab countries by gender, age and economic status over a 20 year period from 1990-2010. As far as we are aware, this is the first such analysis to examine viral-associated HCC in the Arab world using GBD 2010 dataset.

Materials and Methods

The Arab countries

The countries that make up the Arab world were taken from membership of the Arab League (Arab League, 2013). The Arab League consists of 22 countries: Algeria, Bahrain, Comoros, Djibouti, Egypt, Iraq, Jordan, Kuwait, Lebanon, Libyan, Mauritania, Morocco, Occupied Palestinian Territory, Oman, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, United Arab Emirates and Yemen.

Estimation of the burden of mortality from hepatocellular carcinoma

Data files for mortality estimates of all causes of hepatocellular carcinoma (HCC), by world region and by country level for the years 1990, 2005 and 2010 were obtained from the Institute of Health Metrics Evaluation (IHME), University of Washington, Seattle (IHME, 2013). Detailed descriptions of how mortality figures were estimated has been previously published as part of the GBD 2010 study (Murray et al., 2012c; Wang et al., 2012). Briefly, mortality estimates were based on several different sources, including surveys, censuses, sample registration data and vital registration data, and final estimates derived using a range of statistical models (Lozano et al., 2012; Murray et al., 2012c; Wang et al., 2012). All mortality figures and rates were estimated with 95% confidence intervals. Data for burden of liver cancer in the Arab world was collated for the 22 Arab countries and analyzed by age, sex and age-standardized rates for hepatitis B and hepatitis C associated HCC. For analysis of HBV/HCV-associated HCC by economic status, countries were divided into three groups, low income, middle income and high income based on their gross national product per capita, as previously described (Mokdad et al., 2014).

Results

Burden of death from liver cancer by risk factor: Comparison of the Arab world with global trends, 2010

In 2010, mortality from all forms of malignancies was estimated to be 7.977 million (95% uncertainty interval [UI] 7.337-8.403 million). Liver cancer was amongst the top three leading causes of death, accounting for 9.4% (752,101 [95% UI 643,599-880,282]) of the cases. The vast majority of liver cancer deaths were associated with hepatitis B (HBV) (45%) and hepatitis C virus (HCV) (26%) infection. Alcohol associated cases accounted for approximately 20% of the total liver cancer deaths (Table 1). In the Arab world, a total of 17,638 deaths were estimated to be due to liver cancer. Of these, 36% were associated with HBV and 40% with HCV.

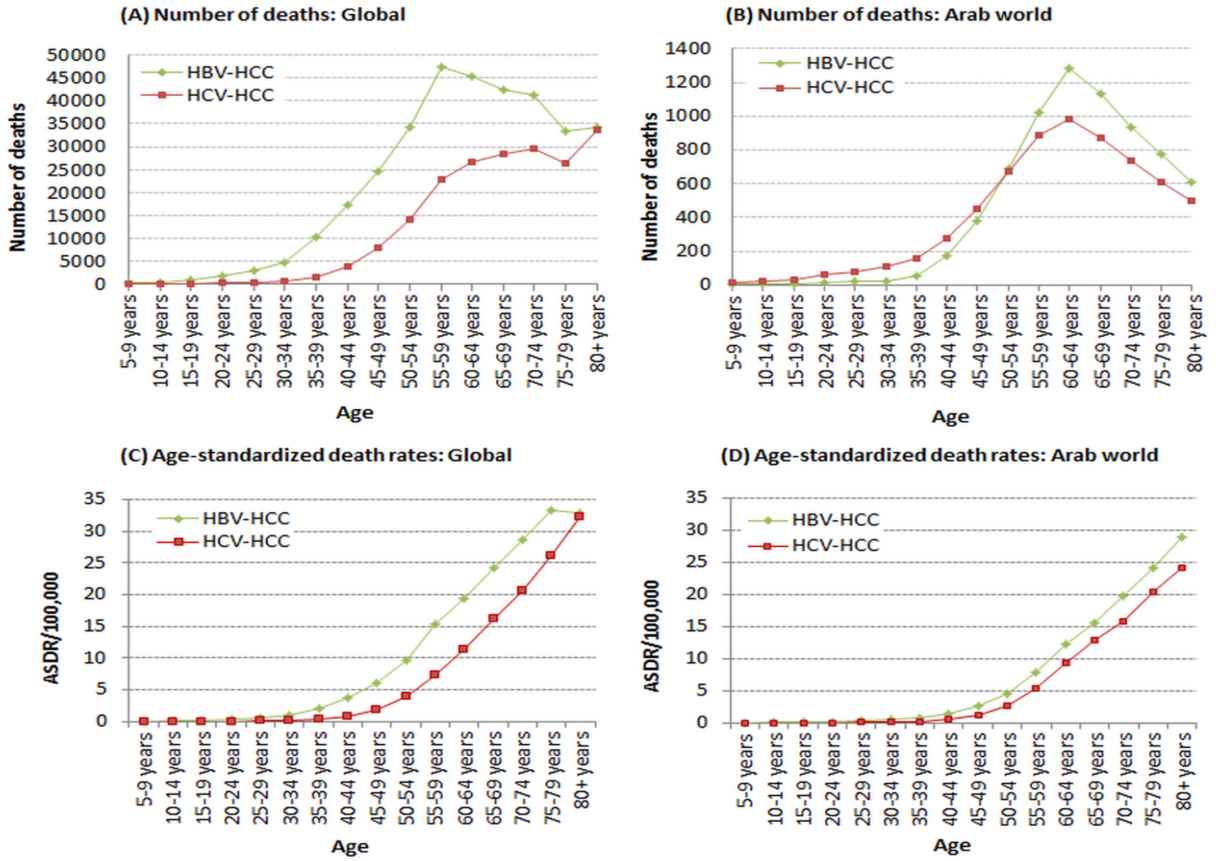

Figure 3. Mortality from HBV and HCV-associated Hepatocellular Carcinoma Globally and in the Arab World by Age, 2010

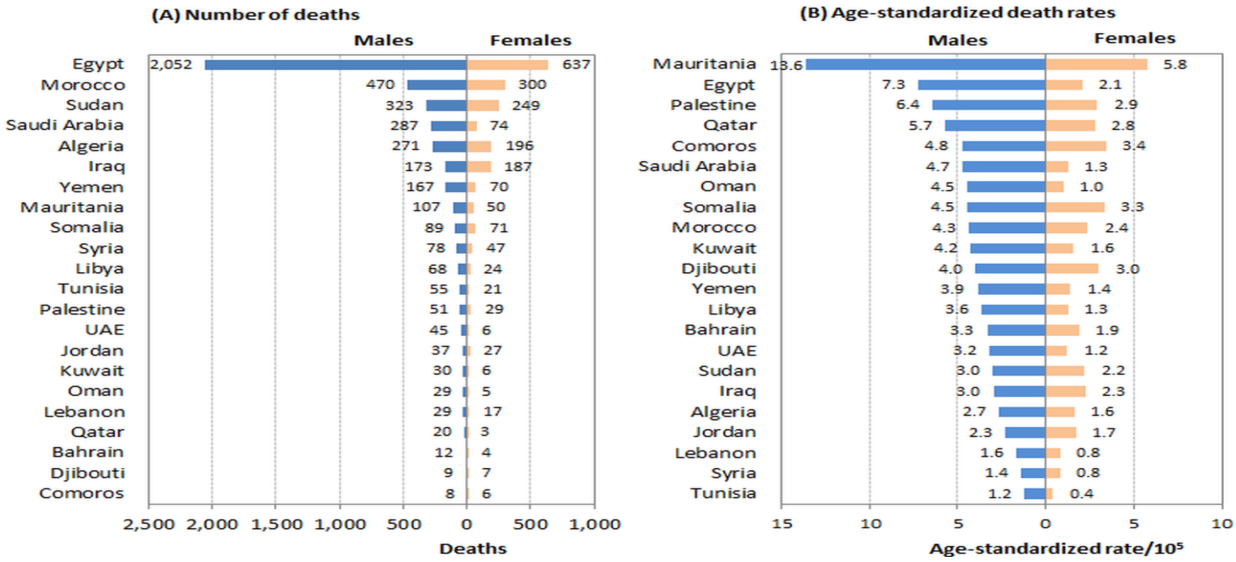

Figure 4. Burden of Mortality from HBV-associated Hepatocellular Carcinoma in Arab Countries, 2010

Alcohol-associated cases accounted for less than 10%. Irrespective of the cause, males from both populations had a markedly higher risk of dying from liver cancer compared to females. For HBV-associated cancer, the male:female ratio was 3:1 in the global population and 2:1 in the Arab population. For HCV-associated liver cancer, male:female ratio was the same for both populations (i.e. 3:2). However, the percentage of deaths from liver cancer associated with HCV in the Arab population was substantially higher than the global percentage (40.3% versus 26.0%) (Table 1).

Burden of death from HBV and HCV-associated hepatocellular carcinoma: Comparison of the Arab world with global trends, 1990-2010

Analysis of the number of deaths and age-standardized death rates (ASDR) for HBV and HCV-associated hepatocellular carcinoma (HCC) over a period of 20 years (1990-2010), revealed that both, the total number of deaths and the ASDR had gradually increased during this interval (Figure 1). This trend was seen in both the Arab and the global population. However, the increases were particularly prominent in the Arab population. In

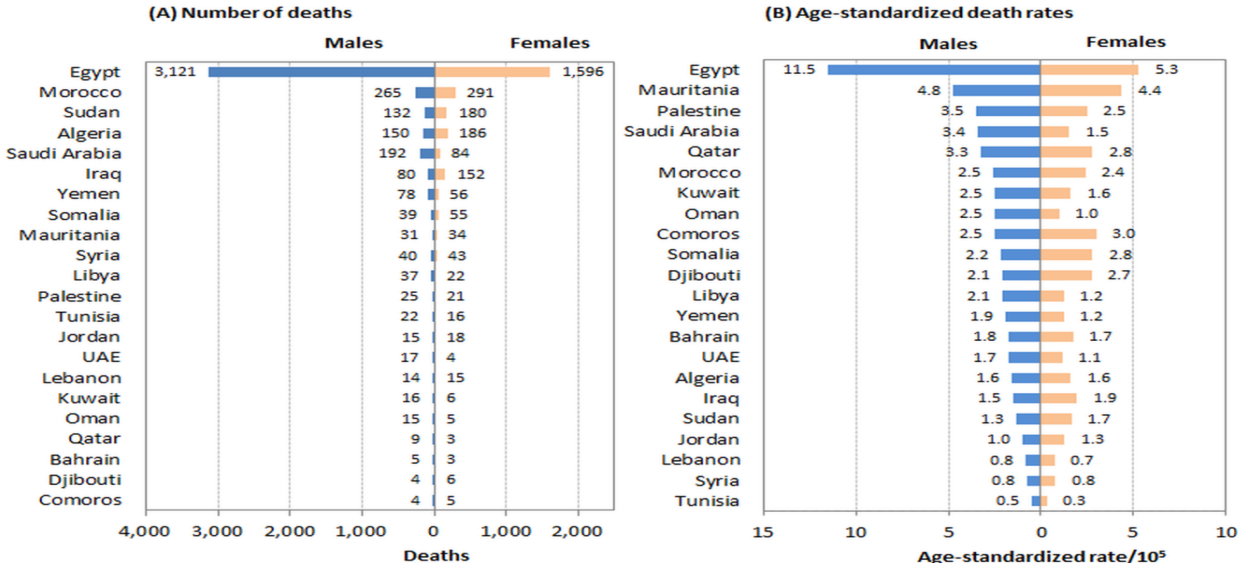

Figure 5. Burden of Mortality from HCV-associated Hepatocellular Carcinoma in Arab Countries, 2010

this population, from 1990 to 2010 the number of deaths from HBV-associated HCC increased by 137.2% and ASDR by 4.1%. For HCV-associated HCC, the number of deaths increased by 215.6% and ASDR by 14.8% over the same period. These figures are approximately twice as high as the global average. To further understand which countries in the Arab world were contributing most to these increases, we examined the percentage change in ASDR from 1990 to 2010 in each Arab country (Figure 2). Of the 22 Arab countries, 7 (Bahrain, Jordan, Lebanon, Mauritania, Saudi Arabia, Sudan and Syria) had reduced their ASDR for both HBV and HCV-associated HCC. Of the countries which had experienced an increase in their rates, Egypt, Kuwait and Libya ranked top.

Burden of death from HBV and HCV-associated hepatocellular carcinoma by age: Comparison of the Arab world with global trends, 2010

HBV and HCV-associated HCC is primarily a malignancy of young adults. Globally, HBV-associated HCC peaked around the age group 55-59 years. In this age group, there were more than 50,000 deaths from HBV-associated HCC worldwide (Figure 3A). In contrast, HCV-associated HCC increased with age, but the overall burden was considerably less than that of HBV-associated HCC in all age groups. In the Arab world on the other hand, the burden of death for both HBV and HCV-associated HCC followed a similar pattern, peaking in the age group 60-64 year olds (Figure 3B). However, no such peaks were observed when ASDR/100,000 was analyzed with age. Both HBV and HCV-associated HCC showed a virtual linear increase in death rate after the age of 50 (Figure 3C and 3D).

Burden of death from HBV and HCV-associated hepatocellular carcinoma by Arab country, 2010

Of the 22 Arab countries constituting the Arab world, Egypt had by far the highest burden of deaths from both HBV and HCV-associated HCC (Figures 4A and 5A). In fact, 41.7% of all HBV-associated HCC and 63.3% of all HCV-associated HCC deaths occurred in Egypt.

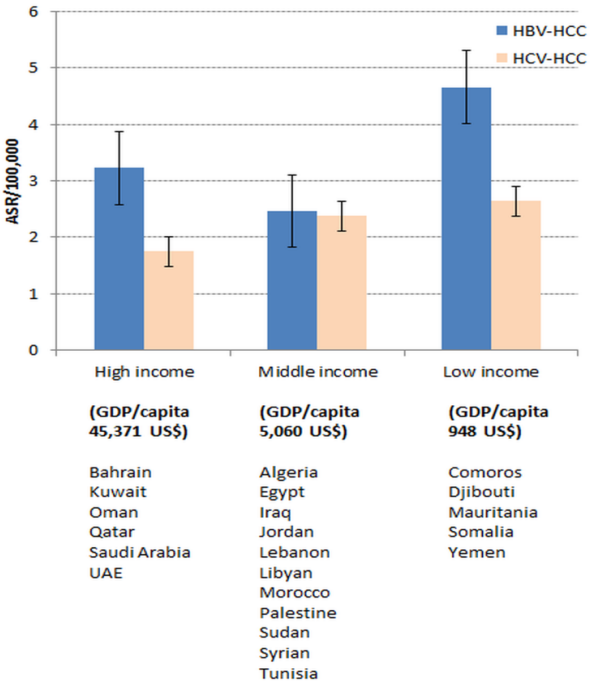

Figure 6. Mortality of HBV and HCV-associated HCC by Income Status in the Arab World, 2010

Moreover, Egypt also had the highest ASDR for HCV-associated HCC in both males 11.5/100,000) and females (5.3/100,000) (Figure 5B). For HBV-associated HCC, Mauritania had the highest ASDR (13.6/100,000 for males and 5.8/100,000 for females) (Figure 4B).

Burden of death from HBV and HCV-associated hepatocellular carcinoma by national income status in the Arab world, 2010

The economic status of the 22 Arab countries is vastly different. On the one hand we have the high income oil rich Gulf countries with an average GDP per capita of 45,371 US$ and on the other hand, the low income countries with an average GDP per capita of just 948 US$ (Arab League, 2013). To determine if economic status has an impact on the ASDR of HBV and HCV-

associated HCC, we divided the 22 Arab countries into 3 groups, as previously described (Mokdad et al., 2014). The general trend indicated that rates were higher in low income countries compared to high income countries. The mean ASDR/100,000 for HBV associated HCC in high income and low income countries was 3.2 and 4.7 respectively. For HCV-associated HCC, these rates were 1.8 and 2.6 respectively (Figure 6). The differences were less obvious between low and middle income or middle and high income countries.

Discussion

The Arab world consists of 22 countries spanning the Middle East and most of North Africa. The total population is estimated to be over 370 million, with Egypt being the most populous (83 million) (Arab League, 2013). Although all Arab countries have some features in common such as language, culture and customs, they differ in terms of their wealth, diet, educational systems and health care services. These differences are reflected in the pattern of diseases observed in these countries (Mokdad et al., 2014; Rahim et al., 2014). In this study we have examined the burden of deaths from hepatitis B and C-associated hepatocellular carcinoma (HCC) in the Arab world and compared it to the global pattern. We have used the dataset from GBD 2010 study, which provides for the first time, estimates of deaths specifically attributable to HBV and HCV-associated HCC. The GBD 2010 data was compiled from a multitude of sources of varying reliability and the limitations of the study have been previously described (Lozano et al., 2012; Murray et al., 2012a; 2012b; Wang et al., 2012).

In 2010 the global number of deaths from HBV and HCV-associated HCC was 341,380 and 195,713 respectively. Of these, 6,447 (1.9%) and 7,111 (3.6%) occurred in the Arab world, with Egypt having by far the largest number of deaths. This burden is partly due to the fact that Egypt has the largest population, but also to the fact that Egypt has amongst the highest prevalence of HBV and HCV infections in the Arab world, and indeed in the world (Salim et al., 2009). For example, for HCV, it is estimated that 10-20% of Egyptians are infected with the virus, more than 3 times the global rate (Daw and Dau, 2012; Frank et al., 2000; Gravitz, 2011). A proportion of chronically infected individuals will go onto develop HCC. In the current study, we found the age-standardized death rate (ASDR) for HCV-associated HCC in Egypt in 2010 to be 11.5/100,000 compared to an average rate of 2.2/100,000 in the Arab world and 3.0/100,000 globally. These high rates have been attributed to suboptimal infection control practices in clinics and hospitals. The reuse of syringes and poor sterilization practices during the campaign to treat schistosomiasis in 70s and 80s has also shown to be partly responsible for the transmission of HCV in Egypt (Frank et al., 2000).

Our analysis also revealed that over the two decades, mortality rates of viral-associated liver cancer increased both globally and in the Arab world. Although the overall ASDR for HBV and HCV-associated HCC are lower in the Arab world as compared to the global rates, the percentage increase in the rates from 1990 to 2010 in the Arab world was almost double of that observed globally (4.1% versus 2.6% for HBV-HCC and 14.8 % versus 7.6% for HCV-HCC, respectively). This clearly indicates that the 73.3% and 215.6% increase in the total number of deaths for HBV-HCC and HCV-HCC in Arab world from 1990 to 2010 is not merely due to an increase in the population growth. Such increases will no doubt place further strain on the already stretched healthcare systems in the region, particularly in the low income countries. Indeed, in low income Arab countries (Comoros, Djiboute, Mauritania, Somalia and Yemen), the mean ASDR for HBV and HCV-associated HCC were significantly higher than in high income oil-rich Gulf states (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia and UAE). Higher mortality rates found in low income Arab countries may partly be due to the lack of availability of effective treatments. The 2012 WHO survey of member states on viral hepatitis noted that only half of the countries had clinical guidelines for the treatment of hepatitis, with fewer still having tenofovir or entecavir listed in their essential medicines (WHO, 2013). Furthermore, just 54.8% had pegylated interferon, the frontline treatment for HCV, listed. Availability of treatment does not translate into provision of care to those most-at-risk especially among remote rural communities and the indigent. Publicly funded treatment is needed for these groups to offset the high cost of HBV and HCV therapy. Other factors that have been implicated to contribute to the higher rates in some of the Arab countries include hemodialysis, nosocomial transmission, intravenous drug abuse as well as, to a lesser extent, dentistry practices, laboratory services, hospital waste handling and habitual/high risk behaviors (Daw and Dau, 2012; Gasim, 2013). Both hepatitis B and C viruses have a latent asymptomatic phase providing an opportunity for screening in high risk populations. However late diagnosis continues to occur and patient compliance with treatment regimen remains suboptimal in many Arab countries (WHO, 2013).

As there is no effective treatment for HCC, prevention of HBV and HCV infection is currently our only real option. An effective vaccine for HBV is available and was recommended by WHO in 1992 to be included in the national immunization programs (Shepard et al., 2006). However, not all countries adopted this recommendation, in spite of the fact that there is now substantial evidence that vaccination for HBV reduces HBV-associated diseases, including HCC (Shepard et al., 2006; Chang et al., 2009; Luo et al., 2012). As for the Arab world, by 2008 all the countries except for Somalia, had implemented this recommendation with most of these countries reaching coverage of over 80% of their target population (Jemal et al., 2011). Only two countries, namely Mauritania and Yemen had coverage rates of less than 80% (Jemal et al., 2011). Both of these countries are amongst the poorest in the Arab world with GDP per capita of less than 1500 US$ (Arab League, 2013). Somalia which has a GDP of less than 300 US$, is additionally ravaged by civil conflict which is also impacting on the limited resources for the healthcare services.

The Arab world faces a looming crisis as both the

total number of deaths and the population adjusted rates are increasing sharply compared to rest of the world. Public health action is urgently needed, particular in Egypt and Mauritania which have the highest rates in the region. A multifaceted approach, from carefully planned awareness campaigns to data-driven public health interventions are needed to prevent viral transmission. Moreover, regional clinical guidelines for screening and treating hepatitis B and C infections should be available, coupled with enhanced access to healthcare services and public funds for treatment. Efforts to improve HBV vaccination coverage at birth are also critical to prevent mother-to-child transmission, a common mode of virus spread in many of these countries (Howell et al., 2014). Unfortunately, in the Arab world, HCV poses an even greater burden and higher rate of rise than HBV; thus prevention efforts against HCV infection cannot rely on vaccination, since no suitable vaccine is available. Targeting infection control measures in high risk settings such as healthcare, dentistry and personal grooming service sectors will help. Modeling of global HCV burden indicates that the currently available medical treatment alone is unlikely to reduce the burden of HCC (Razavi et al., 2014). Continued surveillance using better data collection is also needed in the Arab world to monitor the rising burden and assess the impact of these programs.

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