Epidemiological projections of viral-induced hepatocellular carcinoma in the perspective of WHO global hepatitis elimination

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Abstract
Hepatitis B is an eminent risk factor for hepatocellular carcinoma (HCC) in Southeast Asia and sub-Saharan Africa, whereas hepatitis C is a key risk factor for HCC in Western Europe and North America. Increased awareness of the global burden of viral hepatitis resulted, in May 2016, in the adoption of the first global health sector strategy on viral hepatitis by the World Health Assembly, which calls for the elimination of viral hepatitis as a public health threat by 2030. Although the incidence of liver cancer resulting from viral infections has increased since the 1990s, the implementation of public health interventions, such as hepatitis B vaccination and antiviral therapies might have reduced the global burdens of HCC. Hepatitis B immunization in infancy has been associated with a reduction in the risk of infant fulminant hepatitis, chronic liver disease, and HCC in Taiwan. Achieving viral hepatitis elimination by 2030 can be accelerated by improving the access to HCC screening programs. HCC surveillance programs in developed countries need to be refined to increase an access to personalized surveillance program, whereas the limited access to surveillance and treatment of HCC in developing countries remains a significant public health issue.

Keywords
epidemiology, hepatitis B, hepatitis C, hepatocellular carcinoma, surveillance, World Health Organization

Key points
- The WHO target aims to reduce the incidence of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections by 90% and their associated mortality by 65% by 2030.
- The implementation of vaccination and HBV antiviral therapy might have reduced the incidence rate of hepatocellular carcinoma (HCC) in certain geographical areas.
- High hepatitis B vaccination coverage in infants, but low birth dose coverage in newborns, and low uptake of antiviral prophylaxis in pregnant women, might have increased the proportion of chronic hepatitis B infection attributable to mother-to-child transmission.
- Hepatocellular carcinoma surveillance programs in developed countries need to be refined to increase an access to personalized surveillance program.
1 | INTRODUCTION

Liver cancer is the sixth most commonly occurring cancer worldwide and the fourth leading cause of cancer death in the world. Hepatocellular carcinoma (HCC) is the dominant histological type, comprising 75%-85% of cases of primary liver cancer, followed by cholangiocarcinoma. The main risk factors for HCC are hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol consumption, metabolic syndrome, and exposure to aflatoxin.

The epidemiology of HCC caused by viral hepatitis around the world highlights a real disparity between high-income and low-income countries. Of 520,000 HCC cases secondary to viral hepatitis, 85% are diagnosed in Global South whereas only 15% in Global North. Although in countries with high sociodemographic indexes HBV and HCV account for 18% and 40% of absolute liver cancer deaths, respectively, we observe an inversion in countries with low sociodemographic indexes with the proportions being 35% and 24%, respectively. For several years, national and international public health policies have been developed to counteract the burden of disease brought by viral hepatitis. Notably, United Nations recognized viral hepatitis as a major cause of morbidity and mortality worldwide and targeted in its Sustainable Development Goals in 2015. Subsequently the WHO developed a strategy to eliminate viral hepatitis. Unlike smallpox which was eradicated, the objective is to eliminate HBV and HCV infections as a public health threat. More concretely, the WHO’s strategy aims to achieve a 90% reduction in the incidence of new infections and a 65% reduction in the mortality rates associated with these infections by year 2030.

The goal of this review is to examine the current epidemiological trends of HCC because of viral hepatitis, and to provide projections for the future. Other interventions to accelerate the elimination of HCC are also discussed.

2 | CURRENT SITUATION

2.1 | Epidemiology of HBV and HCV infection

2.1.1 | Global prevalence

The WHO estimates that 257 million people (3.5% of the world’s population), and 71 million people (1% of the world’s population), are affected by chronic HBV and HCV infections, respectively, much higher than the number infected with HIV (37.9 million). High HBV prevalence is observed in the WHO African and Western Pacific regions, accounting for 68% of chronic HBV infections worldwide. By contrast, HCV mainly affects the WHO Eastern Mediterranean Region and European regions, with an incidence rate of 62 per 100,000 inhabitants per year.

2.1.2 | Trends over the last decades

Hepatitis B vaccination has been available since 1982, and has been a main deriver for a reduction in the incidence of new chronic HBV infections in infants. Worldwide hepatitis B surface antigen (HBsAg) prevalence in children under 5 years of age was reduced from 4.7% (pre-vaccination era) to 1.5% (2015).

Taiwan is one of the first countries that implemented the national infant hepatitis B immunization program. The vaccination of newborns of carrier mothers was introduced in 1984 and extended to all neonates, irrespective of maternal HBV status, in 1986. Fifteen years later, Taiwan observed a dramatic decrease in HBsAg prevalence among persons younger than 15 years of age from 9.8% to 0.7% in 1999. Similarly, universal infant HBV vaccination in China has led to a 90% reduction in the prevalence of HBsAg among children aged <5 years in 2009 compared with 1992. In 24 countries in the Western Pacific Region that had introduced infant hepatitis B vaccination program, including the birth dose vaccine, the prevalence of HBsAg in children decreased from 8% in 1990 to 1% in 2012.

 Globally, HBV vaccination resulted in an estimated 83% reduction in the number of new HBV infections (310 million cases) between 1990 and 2020.

A decrease in HCV incidence has been observed since the second half of the 20th century, with a declining seroprevalence in most countries. It is thought that an improvement in the safety of intravascular injections has contributed to reducing the risk of HCV transmission. However, in the USA, an increase in HCV transmission linked to recreational drug uses in the context of an opioid crisis has become an emerging public health concern. Nine countries were estimated to have an important increase in HCV prevalence between 2007 and 2015, because of an influx of foreign workforce from HCV-endemic countries (Qatar and the United Arab Emirates), an increase in rate of iatrogenic infections (Azerbaijan, India, Iraq, Syria and Uzbekistan), or injection-drug use (Iran, Russia).

2.2 | Epidemiology of HCC due to HBV or HCV

2.2.1 | Risk of HCC in the absence of antiviral treatment

In contrast with a sharp decrease in mortalities caused by HIV, mortality from viral hepatitis has dramatically increased from 1.1 million in 2000 to 1.3 million in 2015. Most viral hepatitis deaths in 2015 were due to cirrhosis and HCC. The risk of HCC is estimated to be 14.1 (95% CI: 10.6-18.8) times higher in people with chronic HBV infection than those without chronic HBV infection. In Europe and the USA, the incidence rates of HBV-related HCC were 0.02
per 100 person-years for inactive carriers, 0.3 for chronic hepatitis without cirrhotic, and 2.2 for compensated cirrhosis.\textsuperscript{19} In the majority of HBV-related HCC cases (80%-90%) there is underlying liver cirrhosis.\textsuperscript{20}

The risk of developing HCC is 8.1 (95% CI: 5.0-13.0) times higher among persons infected with HCV than those without HCV.\textsuperscript{18} Once HCV-related cirrhosis is established, HCC develops at an annual rate of 1%-8%.\textsuperscript{21,22} Patients with chronic hepatitis C and bridging fibrosis in the absence of cirrhosis are also at significant risk of HCC.\textsuperscript{23}

Patients with cirrhosis with active HBV or HCV infections had a much higher incidence of HCC than patients with alcoholic cirrhosis without viral hepatitis, even after adjusting for obesity, age, diabetes, and platelet count.\textsuperscript{24}

### 2.2.2 Geographical variation in HCC incidence

According to GLOBOCAN, a tool that predicts the future cancer incidence and mortality burden worldwide, the number of new HCC cases in 2018 was 841 000 (4.7% of all cancers) worldwide.\textsuperscript{1} Of these, HBV is responsible for 360 000 incident cases, with an age-standardized incidence rate (ASIR) of 4.1 cases per 100 000 person-years. HCV is responsible for another 160 000 incident cases, with an ASIR of 1.7 cases/100 000 person-years. In total, 62% of cases of liver cancer are attributable to HBV or HCV.\textsuperscript{25}

The incidence rate of HBV-related HCC is particularly high in East Asia (China, Japan, South Korea). In 2018, there were 270 000 cases in this area (75% of cases worldwide), including 250 000 cases in China (69% of cases worldwide) (Figure 1).\textsuperscript{4} ASIR was 10.5/100 000 person-years in East Asia (11.7 in China). Interestingly, ASIR in sub-Saharan Africa (2.6/100 000 person-years) was much lower than in East Asia despite a higher prevalence of chronic HBV infection in Africa. This regional disparity (higher HBV prevalence but lower HBV-related HCC incidence in sub-Saharan Africa compared to East Asia) might be related with a difference in major HBV genotypes, a difference in major mode of transmission (more mother-to-child transmission in Asia than in Africa), or difference in exposure to other risk factors such as alcohol consumption.\textsuperscript{26,27}

Regarding the HCV-related HCC, the number of incident cases is also the highest in East Asia where 40 000 new cases occur annually, with an equal distribution between China and Japan.\textsuperscript{4} ASIR was 1.5/100 000 person-years in East Asia (0.9 in China and 4.1 in Japan). Although the absolute number of incident cases is not as high as in East Asia, North Africa has the highest ASIR (12.0/100 000 person-years), followed by North America (ASIR: 3.3/100 000 person-years). HCV is the dominant cause of HCC in Egypt, and is responsible for 84% of HCC, whereas HBV is dominant in other African countries and responsible for 55% of HCC cases.\textsuperscript{28}

Between 1990 and 2016, the estimated annual percentage change, a widely used measure of the ASIR trend, in HBV-related HCC ASIR was 0.22% (Figure 2).\textsuperscript{29} This increase mainly concerns Australia and North America. In addition, the absolute number of HBV-related HCC increased by 106.6% worldwide.\textsuperscript{4} Age-standardized incidence rate of HCV-related HCC increased by 0.57% between 1990 and 2016, and was most marked in the Netherlands, followed by Australia and the UK.\textsuperscript{29} The absolute number of HCV-related HCC also increased in all regions of the world (127.9%).\textsuperscript{29} However, recent study in the USA reported that the rate of HCC incidence began to decelerate around 2007.\textsuperscript{30} Following the introduction of various public health policies, HCC incidence has been decreasing in Japan, since the 2000s.\textsuperscript{31,32}

### 2.2.3 Regional differences in the age of HCC diagnosis

Hepatitis C virus-related HCC cases are generally diagnosed at 60 years of age in all regions of the world, whereas HBV-related HCC is typically diagnosed at a younger age.\textsuperscript{25,26} This inconsistency can be explained by a difference in the mode of transmission/age of infection and natural history of chronic infection.\textsuperscript{33} Furthermore, in sub-Saharan Africa, the median age of diagnosis of HBV-related
HCC (38.9 years) is younger compared with West Pacific region (54.5 years). This variation may be related with a difference in exposure to biological factors such as aflatoxin, but may simply reflect the difference in age distribution of the underlying population (median age of whole population is much younger in African than in Asia). The average age of HCC diagnosis in one area can be changed over time. In Taiwan, after the implementation of the infant vaccination program the average age of HCC diagnosis has increased, reaching a median age of 61 years, similar to that of the USA.

2.3 | Prevention of HCC

2.3.1 | Hepatitis B vaccination

According to WHO, between 1990 and 2015, the coverage of three doses of hepatitis B vaccine in infants (HepB3) has increased from 1% to 85%, with 189 countries that had integrated the infant hepatitis B vaccination in the national program by the end of 2019. However, in many of these countries the first dose of hepatitis B vaccine is given at the age of 6-8 weeks of life, as a combined vaccine with diphteria, pertussis, tetanus, and haemophilus influenzae type B.

Since 2009, in addition to two or three doses of infant vaccines, WHO recommends that all infants should receive the first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours, to prevent mother-to-child transmission and early horizontal transmission of HBV. This so-called “hepatitis B birth dose vaccine (HepB-BD)” still suffers from a low coverage. In 2019, it is estimated that the global coverage of HepB-BD is only 43%, and this is particularly low in the WHO African Region (6%).

Mother-to-child transmission is not only the risk factor for chronic HBV infection, but also the risk factor for liver diseases including HCC. Those who established chronic HBV infection through perinatal mother-to-infant transmission were found to be more likely to maintain persistent viral replication, and have higher risk of HCC and chronic liver diseases than those who established chronic HBV infection through horizontal transmission. This is one of the important rationales why we need to prevent mother-to-child transmission. To reduce the incidence of HBV-related HCC, it is essential to improve the coverage of timely administration of HepB-BD and to efficiently prevent the mother-to-child transmission.

2.3.2 | Aflatoxin control

Aflatoxin is a food contaminant produced by the fungi Aspergillus flavus and Aspergillus parasiticus species which are especially abundant in areas of the world with hot, humid climates. Exposure to aflatoxin B1 is a risk factor for developing HCC in patients with chronic HBV infection. The odds ratios for combined effects of chronic HBV infection and aflatoxin exposure increased to 73.0 (95% CI: 36.0-148.3), when the odds ratio is 6.37 (3.74-10.86) for aflatoxin exposure alone, and 11.3 (6.75-18.9) for chronic HBV infection alone. These estimates indicate that the effects of aflatoxin exposure and chronic HBV infection on HCC risk combine multiplicatively.

2.3.3 | Antiviral therapy

The rise in uptake of antiviral therapies over the past decade might have played a role in decrease in HCC incidence. The main goal of antiviral therapy in patients with HBV is to limit the progression of liver disease, and to prevent the development of HCC. Both of these goals are achieved through the long-term suppression of HBV viral load. Both entecavir and tenofovir disoproxil fumarate reduce the risk of HCC, but do not eliminate its risk. A recent systematic review has found that a risk of HCC was similar between those treated with entecavir and tenofovir.

The eradication of HCV can induce a reduction in HCC by preventing progression to cirrhosis, via the induction of hepatic fibrosis regression in cases of undetectable viral load. Antiviral therapy lead to a reduction in the number of patients with HCC in subjects with HCV. The relatively recent introduction of direct-acting antivirals (DAAs) to the market in 2012 hinders any assessment of their long-term impact in the reduction of the number of HCC cases at the population level.

2.3.4 | Screening for HCC

Antiviral therapy against HBV and HCV diminishes the risk of HCC, but does not completely eliminate this. Therefore, there is a still role of HCC surveillance to identify early-stage cancer that allows a curative therapy to prevent a death from HCC. Indeed, there is an association between the compliance with HCC...
surveillance and longer survival rates in patients with HCV- or HBV-associated compensated cirrhosis.\textsuperscript{58} Western recommendations support a 6-month screening interval, based on HCC volume doubling-time.\textsuperscript{59,60}

In Caucasian HBV cirrhotic patients, the introduction of nucleoside analogue treatment reduced the incidence of HCC during the first ten years from 3.22% to 1.57%.\textsuperscript{61} Subsequently, both the European Association for the Study of the Liver and the American Association for the study of Liver Diseases recommend that HCC surveillance should be continued for at least 10 years in HBV cirrhotic patients irrespective of whether the antiviral treatment was initiated.

All the international guidelines recommend the HCC surveillance in patients with HCV-related cirrhosis, regardless of whether they have completed the DAA or not.\textsuperscript{22,62,63} However, there is a wide variation in the recommendations for patients with F3 fibrosis according to the guidelines.\textsuperscript{64,62,22,63} Despite viral clearance, patients with comorbidities are predisposed to develop cirrhosis following SVR.\textsuperscript{65} Moreover, the difference in terms of non-invasive measurement of liver fibrosis between advanced fibrosis and cirrhosis is very small, and failing to recognize the transition between two stages may lead to the exclusion of some patients who would benefit from the surveillance programs if the HCC surveillance is only indicated for those who have cirrhosis. For these reasons, a pragmatic suggestion is to keep all F3 patient in HCC surveillance programs.\textsuperscript{66}

3 | FUTURE SITUATION

3.1 | Future trends in HBV and HCV incidence

Nayagam et al generated a model predicting the epidemiological evolution of HBV infection according to the preventive interventions.\textsuperscript{11} In the status quo scenario, in which the infant vaccination coverage and HepB-BD coverage are less than 90%, the coverage of peripartum antivirals for HBeAg positive mothers is at 0% and the access to treatment continues at the current levels, an estimated 63 million new cases of chronic HBV infection and 17 million deaths attributable to HBV would occur in the next 15 years. Improving the HepB3 coverage of >90%, without any additional measures, would avert 4.3 million new infections between 2015 and 2030 compared with the status quo scenario. However, the number of HBV-related deaths would paradoxically continue to increase, and this might reach a peak in 2034 with an estimated 1.1 million deaths/year. In addition to the increase in the HepB3 coverage of >90%, providing HepB-BD in 80% of neonates, peripartum antiviral prophylaxis in 80% of hepatitis B e antigen (HBeAg)-positive pregnant women, and antiviral therapy in 80% of adult patients with chronic HBV infection who are eligible for antivirals, would contribute to meet the WHO’s elimination goals by 2030, through avoiding a total of 7.3 million HBV-related deaths, including 1.5 million deaths from HBV-related HCC. However, time needed to reach these goals differ considerably between the countries; half of all regions plan to reach 90% reduction in incidence of new infections before 2060, by implementing the interventions described in the above models.\textsuperscript{11} The other half would reach elimination of new incident chronic infections after 2060.

For HCV infection, the status quo scenario, defined by no change from the diagnosis and treatment rates at their 2016 values and no reduction in general or PWID population risk, would result in only a small decrease in the number of new HCV cases by 2050.\textsuperscript{67,68} Although the total number of chronic infections would fall from 69 to 58 million cases, the incidence of chronic HCV infection would decrease from 227 to 198 infections per one million people by 2060. Blood safety, infection control and harm reduction improvements would meet the HCV elimination criteria for the new HCV infections by 2030. Moreover, implementing these measures with a diagnostic coverage of >90% of infected patients and DAA uptake of 100% would lead to a 61% reduction in mortality by 2030. To achieve a 65% decrease in mortality, more than 95% of patients with chronic HCV infection would have to be diagnosed. Finally, the HCV epidemic among PWID has a critical role in determining whether the elimination target for the new infections is met.

This modeling study should be counterbalanced with results by region. The downward trend in the number of new chronic HCV infections is reflected in specific control policies, particularly in Egypt. Recognizing the healthcare and economic burdens of HCV, Egypt created the National Committee for Control of Viral Hepatitis in 2006. Coupling a screening and treatment policy with a 20% decrease in the incidence of new infection might result in a reduction in the number of chronic HCV infection from 6 million in 2014 to 280,000 in 2030.\textsuperscript{69} According to Polaris Observatory and the European Union HCV Collaborators, Europe is on track for WHO Elimination Targets in 2030 whereas the USA will not.\textsuperscript{70,71} However, among 45 high-income countries, only 9 of these countries (Australia, France, Iceland, Italy, Japan, South Korea, Spain, Switzerland, and the United Kingdom) are likely to achieve hepatitis C elimination by 2030, as targeted by the WHO.\textsuperscript{72} Lack of source of HCV infection in countries where data are not of high quality makes it difficult to do accurate predictions.

3.2 | Future trends in HCC incidence

GLOBCAN predicts an increase in HCC incidence over the coming decades from 841,000 in 2018 to 1.4 million in 2040, paralleled by an increased mortality rate of 780,000 in 2018 to 1.3 million in 2040.\textsuperscript{73} Compared with 2018, HCC incidence in 2030 should be higher in most countries except in Japan, China, and Singapore.\textsuperscript{73} The WHO estimated that 5 million HBV-related or HCV-related HCC deaths occur between 2015 and 2030.\textsuperscript{74} There are several factors which modify the future prediction, such as an increase in the prevalence of metabolic syndrome, as well as population aging and growth.

According to Valery, only a few countries, including Japan and China, will experience a decrease in HCC of any etiology incidence
of around 2% in both sexes until 2030.73 Zheng et al. forecast a decrease in incidence and mortality in China by more than 44% by 2030.73 The expected decreases in HCC incidence are explained by both a decrease in incidence of chronic HBV infection, as well as a decrease in the level of exposure to aflatoxin B1 in the population.66,67 Considering that HCC incidence increased fivefold between 2004 and 2014, HCV-related HCC incidence could also probably increase in the future without a change in public health policy.77 In addition, economic and industrial development might lead to the westernization of Chinese etiological factors.78 Diabetes prevalence is high around 10.9% in the Chinese population in 2013.79 Non-alcoholic steatohepatitis is becoming an emerging cause of chronic liver disease in China.80,81 Thus, though the burden of HBV on HCC is likely to reduce in the next decades, this might be counteracted by the increasing burden of metabolic syndrome.

Predictions for Japan show a decrease in the incidence of HCC cases with a 48% decrease in men and a 26% in women by 2030.73 This reduction in incidence is explained by demographic transitions with an increase in aging population, as well as by public health interventions. From 1996 to 2014, the cost of illness which represents the social burden of HCC trended downward, mainly linked to a drop-off in costs linked to mortality.82

In Europe, HCC mortality rates are forecast to increase in Northern and Eastern Europe, because of high chronic HCV infection prevalence in the population born between 1960 and 1980, together with low HBV vaccination coverage.83 Mortality from HCC in southern European countries is expected to decrease as a result of antiviral control policies.

In the USA and Australia, HCC incidence is predicted to increase until 2030 because of immigration from Asia and Pacific islands with high prevalence of HBV and HCV,84 together with an increase in the incidence of metabolic syndrome.85 In the USA, although the prevalence of alcoholic cirrhosis remained stable between 1995 and 2013, the incidence of HCV cirrhosis saw an increase between 1999 and 2012. Ahmed’s model suggests that NASH prevalence exceeded HCV prevalence in 2006, and NASH’s contribution to HCC overtook HCV-related HCC in 2015 at an approximately 25 million persons.86 In 2025, the number of HCV-infected people is predicted to reach 1 million, whereas the number with NASH will reach 17-42 million, according to the model used. Between 45 000 and 106 000 cases of CHC-NASH are expected to occur in 2025, compared with 18 000 HCV-related HCC cases.

Globally, HCV mainly affects patients of a certain age. Most of the HCV in the USA comes from the population born between 1945 and 1965.87 In countries like Italy, Japan, and Egypt, the age-specific distribution of HCV-patients is even more skewed toward old age.88,89,90 But the efficacy, safety, and tolerance of AADs have made it possible to prescribe these treatments widely to the elderly. In France and England, treatment for HCV is prescribed to a population of average age 55 years.84 But elderly patients are more likely to have advanced liver disease and progressive liver damage from viral infection.91 Thus, HCV eradication mainly concerns an elderly population at risk of developing HCC in later years.

### 4 | OTHER INTERVENTIONS TO ACCELERATE THE ELIMINATION OF HCC

The main priority to reaching elimination goals is to identify strategies to increase the timely administration of HepB-BD while also improve coverage rates of infant vaccination (HepB3). WHO’s Strategic Advisory Group of Experts has made recommendations for strengthening national vaccine programs, including advocating for stronger national leadership and commitment, securing investments, and enhancing surveillance and accountability mechanisms.92 The priority is to improve immunization coverage, but this has no impact for those living with chronic HBV infection. Thus, monitoring of HCC should be routinely offered to these patients at increased risk of HCC. Improving in access to HCC surveillance could potentially increase detection of HCC at a localized stage and overall survival.

#### 4.1 | Prevention of infections

##### 4.1.1 | Prevention of HBV mother-to-child transmission

Before the wide implementation of infant hepatitis B vaccination programs, the major mode of HBV transmission was horizontal transmission between the children.11,26 However, thanks to an increase in coverage of infant hepatitis B vaccination (HepB3) that effectively prevented horizontal transmission but not mother-to-child transmission, the latter has become a major mode of transmission worldwide. Increasing the coverage of HepB3 alone would certainly result in the reduction in HBsAg prevalence in future mothers. Nevertheless, in comparison with women who developed chronic HBV infection through horizontal transmission, women who developed chronic HBV infection through MTCT are more likely to maintain persistent viral replication with positive HBeAg well into their reproductive age, which makes themselves more prone to replicate MTCT.93,94 This indicates that unless HepB-BD is integrated, increasing the coverage of HepB3 alone would not be enough to eliminate MTCT. Indeed, a modeling work estimated that the proportion of chronic HBV infection due to mother-to-child transmission is expected to increase worldwide from 16% in 1990 to 50% in 2030.11 Timely administration of HepB-BD as soon as after birth, preferably within 24 hours, could efficiently prevent mother-to-child transmission.95 However, the access to the HepB-BD remains uneven. In 2015, the American and Western Pacific Regions were the only regions with a HepB-BD coverage exceeding 70%. In the African region the coverage was only 6%.69 This is because (a) only a few African countries have integrated HepB-BD in the national vaccination program; and (b) its timely administration is not sufficiently made even
in countries that have integrated HepB-BD in their national program due to high rate of child birth at home. 97

Furthermore, HepB-BD is not perfect to prevent mother-to-child transmission from a high-risk mother. HBeAg-positive mothers exhibit a 20% risk of transmission to their offspring, despite neonatal immunoprophylaxis using HepB-BD. 98,99,100 In a resource-rich country, co-administration of hepatitis B immune globulin (HBIG) to these neonates has been done to further reduce the risk, but HBIG is not highly accessible in sub-Saharan Africa due to its high price and limited supply. 37 Recently the WHO issued a new recommendation that HBV-infected pregnant women with high viremia (>200,000 IU/mL) should be treated using tenofovir during their pregnancy to reduce the risk of mother-to-child transmission, in addition to three doses of infant hepatitis B vaccine including HepB-BD. 42 The application of this new recommendation, however, would require some additional optimization in low-income countries where there is no PCR assay to quantify HBV DNA levels or HBIG. In areas with a limited access to HBV DNA assay, HBeAg can be alternatively used to identify high-risk pregnant women who would benefit from peripartum antiviral prophylaxis. 101 In places where there is no HBIG, the efficacy of tenofovir during pregnancy to prevent mother-to-child transmission is unknown, because most of the studies that evaluated the efficacy of peripartum antiviral prophylaxis were conducted in China, where both HepB-BD and HBIG were systematically provided to all the neonates. It is therefore urgent to evaluate the efficacy of “HBIG-free” strategy. 102

4.1.2 Reducing the transmission of HCV

There are still 1.75 million new cases of HCV annually in 2015. 6 Unsafe health-care procedures, and the use of injection drugs, are the two principal modes of HCV transmission. The former—unsafe health-care procedures—is the predominant transmission route in the Eastern Mediterranean Region, whereas in Europe, injection drug use poses the major problem. 103,104,105 The proportion of unsafe injections worldwide, with respect to safe injections, was estimated to be 39% in the year 2000, and fell to 5% in 2010. 6 In the Eastern Mediterranean and South-East Asian regions, needles are still commonly used without being sterilized. The distribution of sterile syringes and needles to drug users is anticipated to reach target levels of 300 per person per year in 2030, instead of 27 in 2015. 6

4.1.3 Increase in awareness and uptake of preventive measure

According to the WHO, improving diagnosis and access to treatment is a key to reducing mortality rates from viruses infection. 106 In 2015, among 257 million people living with HBV infection, only 9% (22 million) knew of their status. Among that population, 8% (1.7 million) were treated. 6 Regarding chronic HCV infection, only 20% (14 million) know their status. 6 In America, status is known by 36% of patients, whereas by only 6% in Africa. 6 A public health approach is needed, without anyone left behind, including certain high-risk groups for HBV and HCV infection, such as prisoners, migrants, persons who inject drugs, men who have sex with men, and those living with HIV infection.

4.2 Prevention of HCC

4.2.1 Disparities in access to HCC surveillance

Although biannual HCC monitoring is recommended, screening is only partially applied to the target populations, even in wealthy countries. Less than 30% of cirrhotic patients with hepatitis B and hepatitis C were included in HCC surveillance programs. 107,108 Only 12% of HCV patients with cirrhosis received at least 2 years of routine follow-up surveillance. 109

Access to healthcare appears to impact the uptake of screening for HCC in developed countries. In the USA, lower HCC surveillance rates were apparent among African-Americans and underinsured patients, reflecting racial and socioeconomic disparities. 110,111

In the USA, low rates of screening of the at-risk population are perhaps explained by a lack of awareness of the recommendations amongst primary care providers, who follow the majority of cirrhotic patients. 112,113 Gastroenterology visits nearly tripled the odds of imaging, but primary care visits did not. 114 To improve surveillance rates in cirrhotic patients, efforts should target both improved care in primary facilities and facilitating access to sub-specialty care.

Hepatocellular carcinoma surveillance receipt was significantly higher in patients who knew cirrhosis is a risk factor for developing HCC and significantly lower in those reporting barriers to surveillance, including costs of surveillance testing. 115 These reasons indicate the need for interventions, including provider or patient education, to improve HCC surveillance effectiveness in clinical practice (Figure 3).

4.2.2 Emergence of personalized management

HCC risk stratification according to viral etiology

For HBV, various scoring systems have been proposed to define distinct HCC risk categories. Applied to the Caucasian population, PAGE-B (platelets, age, gender) allows the identification of a category of patients with a low risk of HCC without exceeding the threshold risk of 0.2% per year. 116 On the other hand, patients with a medium or high risk of HCC, according to the PAGE-B classification, should benefit from screening. 22 Other scoring systems exist in Asia such as GAG-HCC, CUHCC, and REACH-B, which use similar prognostic variables.

For HCV, many patients have been already treated or will be treated with DAAs. However, most patients treated at an early stage of liver fibrosis had a HCC risk under the accepted thresholds for surveillance. Identification of patients with a low cumulative risk at 3 years of HCC
could prevent superfluous HCC screening during the first 3 years after SVR. Machine learning algorithms may prove to be effective in determining the risk of individual HCC by revealing complex interactions between predictors of cancer. Patients with HCV who achieved SVR and had both a low AST value and a high prothrombin time after viral eradication had a low likelihood of developing HCC. Other tools such as Fibroscan or predictive biomarkers are currently being studied to predict the incidence of HCC in patients with hepatitis C. The future challenges include the successful incorporation of genetic information into clinical risk models and taking into account environmental risk factors assessed in large prospective cohorts.

New HCC surveillance modalities in high-risk individuals despite viral eradication or control

Ultrasound remains a first-line tool for detection as it is inexpensive, widely available, and safe (sensitivity 84%). Restricting the efficacy of ultrasound is its low sensitivity for early stage HCC detection, which is just 47%. A combined approach utilizing ultrasound together with the AFP marker is associated with an increase in sensitivity in early-stage HCC detection (sensitivity 63%).

A significantly higher HCC detection rate using MRI compared with ultrasound was shown in a cohort study in which the majority (71%) of patients had developed cirrhosis from HBV. Most of the cancers detected by MRI scans were at very early stages with favorable survival rates in patients. However, monitoring by MRI is limited by the high cost, which explains that currently international guidelines do not endorse MRI as a screening tool. Nevertheless, ongoing studies dedicated to cost-effectiveness evaluation in patients bearing the highest residual HCC risk following HBV control/HCV eradication might reveal if such personalized strategy could be implemented in the future.

There is a growing interest in serum biomarkers which could improve sensitivity in detecting early-stage HCC. The current trend focuses on the association of several biological values such as the Adjusted Serum Alpha-Fetoprotein—Based Algorithm, or the GALAD score. In a multinational phase 2 study, the detection of early HCC using GALAD reached a sensitivity of 60%-80%.

4.2.3 | Improve in access to HCC surveillance in sub-Saharan Africa

Most sub-Saharan African countries do not have any surveillance program for HCC. Therefore, the vast majority (84%) of HCC patients in Africa are diagnosed at a late, multifocal disease stage with a mean tumor size of 8 cm and a median survival of 2.5 months. There are obstacles at several levels. First, the access to abdominal ultrasound and skilled examiner is highly limited in Africa, especially in rural areas. Second, the curative procedures, such as liver resection, percutaneous ablation, or transplantation, are still scarce in these countries. In a large case series of HCC in sub-Saharan Africa, only 3% of patients received specific treatment for HCC. Third, even palliative care, which should not require a large investment, has been poorly provided in the continent.

A national cancer program has been successfully developed in a few sub-Saharan African countries, such as Rwanda and Nigeria.
Other countries, like Uganda, have been trying to develop HCC surveillance programs, but are facing difficulties to establish optimal linkage to care and to expand capacities to treat HCC.\textsuperscript{128}

To generate effective public health policies and to optimize the mobilization of resources, it is essential to have an accurate estimate of the incidence rate and mortality rate of HCC, as well as its cause. However, the data are missing unfortunately in these low-income countries, leading to an underestimate of HCC disease burden.\textsuperscript{129}

\section{LIMITATION OF THE REVIEW}

The major limitation of the current review is that our discussion was broadly based on the epidemiological data that were made available by the GLOBOCAN, WHO, Global Burden of Disease, and other modeling studies. Unfortunately, the quality of these data might not be ubiquitously high, especially the estimates for some resource-limited geographical regions might be highly questionable. For example, many cancer registries have not adopted the current clinical diagnostic criteria for HCC and still only rely on histology for the classification. In such a context, the genuine HCC incidence could be much higher than that reported by the cancer registry.\textsuperscript{130,131} Moreover, the validity and completeness of registry data might be questionable in some low-income countries, because of missing data, miscoding of liver malignancies as primary liver cancers, or lack of diagnostic capacity.\textsuperscript{129} It is estimated that about 24\% of the world population was covered by population-based cancer registries in 2010, with lower coverage in South America (19\%), Asia (15\%), and Africa (13\%).\textsuperscript{132,133}

Mortality statistics are collected and made available by the WHO.\textsuperscript{134} In 2010, only one-third of the world population was estimated to be covered by the official mortality statistics. Although almost all countries in the Europe and the Americas have comprehensive death registration systems, most African and Asian countries do not.\textsuperscript{135} Since 2010, the Global Burden of Disease project has developed a new method to estimate mortality from HBV and HCV infections, which uses a combination of data from two types of sources: the "mortality envelope" from vital registration, and the "attributable fraction" generated by clinical centers. This method has been employed by the GBD, IARC, and the WHO. Estimating the burden of cancer attributable to infection could help to raise awareness and inform recommendations for action.\textsuperscript{6} However, because of changes in data sources, comparisons with previous results are not possible and estimates are still limited by scarcity of local data, especially in low-income countries.

\section{CONCLUSION}

Hepatitis B and hepatitis C viruses are the third and fourth most common infectious causes of cancer, after Helicobacter pylori and human papillomavirus. Although the incidence of HBV-related HCC and HCV-related HCC has increased since the 1990s, the implementation of HBV measures, such as hepatitis B vaccination and anti-HBV therapy, has reduced the burden of HCC. Nevertheless, the burden of viral hepatitis and HCC is likely to increase over the coming years, caused by an increase in worldwide population.

The WHO aims to eliminate viral hepatitis by 2030. Achieving this objective is conditional on the improvement in the access to vaccines and antiviral treatments, but also the screening programs for HCC which have been adapted to national specificities. Emergence of personalized management concerns developed countries and includes both risk stratification according to viral status and new monitoring modalities in patients at high risk of HCC despite eradication or viral load control. Increasing access to HCC surveillance programs in low-income countries remains a public health issue. Developing HCC cancer control plans in Africa has started in several countries and should be encouraged.

\section{CONFLICT OF INTEREST}

The authors declare that they have no conflict of interest.

\section{DISCLOSURES}

Dr Nahon has received honoraria from Abbvie, Bayer, Bristol-Myers Squibb, and Gilead. He consults for Abbvie and Bristol-Myers Squibb.

\section{DATA AVAILABILITY STATEMENT}

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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