Evaluating the Association between HBV Vaccination Coverage and the Incidence of Liver Cancer at a Global Level

Mohamed Albirair

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Committee:

Mohsen Naghavi (chair)

Charbel El Bcheraoui

Wisal Hassan, MBChB

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ABSTRACT

Background: Liver cancer today is the second most common cause of cancer-related death and ranks sixth most incident cancer worldwide. The most prevalent histopathological type of liver cancer is hepatocellular carcinoma (HCC). The most common cause for HCC is HBV, and it contributes to 50%-80% of HCC around the world. HepB vaccine was introduced in 1982 and incorporated to the Expanded Programme of Immunization (EPI) in 1992. The vaccine has proven to be associated with a reduced liver cancer incidence in studies from Taiwan, The Gambia and China. We aim to study the same association at a global level

Methods: We collected data on HepB vaccine coverage for children less than 1-year old for 195 countries from the WHO, reported in percentages for every year starting from 1989 to 2013. We also collected data on liver cancer incidence rates for 5-year age groups (starting from 5-9) for 188 countries from the Institute of Health Metrics and Evaluation (IHME) reported in number of cases per 100,000 population for every year from 1980 to 2013. We created overlapping, consequent 5-year HepB vaccine coverage rates from the WHO data, calculated the median for each and matched with the respective cohort in the IHME data. For the statistical analysis, we chose the generalized linear latent and mixed model (GLLAMM). We used Microsoft Excel, R and Stata for our data management and analysis.

Results: Overall, we had 2,129 birth cohorts form 153 countries. All observations were in 5-year age groups (5-9, 10-14, 15-19 and 20-24). Among 5-24 years, higher 5-year median vaccination coverage rates by 10% were associated with a relative risk that is lower by a factor of 0.948 cancer incidence after adjusting for age group and year of observation (95% CI: 0.916, 0.982).

Conclusion and recommendations: Higher HepB vaccine coverage rates were associated with lower liver cancer incidence rates. We recommend that future studies evaluate this association at older age groups in order to demonstrate a larger effect size.

PROBLEM AND RATIONALE

Liver Cancer

Liver cancer today is considered the second most common cause of cancer-related death and has the sixth highest incidence among other cancers worldwide.[1] Liver cancer is the fifth most common cancer in men (523,000 cases/year) and the seventh most common cancer in women (226,000 cases/year), accounting for 7.9% and 6.5% of all cancer, respectively.[2] The most prevalent histopathology of liver cancer is hepatocellular carcinoma (HCC) compared to cholangiocarcinoma, hepatoblastoma and angiosarcoma.[2-4] Broadly, across the different age groups, HCC accounts for between 70% and 90% of liver cancer.[5-7] Since HCC is the predominant primary liver cancer (PLC) globally, epidemiology of PLC in general reflects that of HCC.[7] In general, males are more affected by HCC than females,[6] with male:female ratios averages ranging between 2:1 and 4:1.[5] This gender-based difference is attributed to biological differences in exposures to the different risk factors. Characteristically, HCC has unique features of showing temporal trends, marked variation among different population groups, and most importantly, the presence of potentially preventable environmental risk factors.[5] This regional variation in HCC incidence largely reflects the geographical variations in prevalence of risk factors for HCC.[7] Around 80%-85% of the cases are in the developing world.[2,6] The regions most commonly affected by HCC are Sub-Saharan Africa and Eastern Asia.[2,5] Around 50% of the world's cases are in China.[5] HCC can be diagnosed starting from as young as 6 to above 80 years old. Overall,[8] and its global incidence peaks around the sixth decade of life.[9,10] The age of onset of HCC is much younger in Africa and Asia, with a median of 40 to 50 years.[9,11]

The most common causes for HCC are Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections,[3,4] as well as exposure to aflatoxins (aflatoxin B1 or AFB1) from stored food.[3] HBV is the leading cause of HCC worldwide.[5] It contributes to 50%-80% of HCC around the world, and this proportion is higher in some parts of the world like Asia and Africa,[12] whereas HCV is responsible for 10%-25% of HCC cases.[7] However, co-infection with the two viruses lowers the threshold for developing HCC.[7] From an epidemiological point of view, the higher prevalence and longer duration of chronic HBV (CHB) infections especially in parts of the world where HBV is common account for the greater risk for developing HCC.[2,9] Studies have attributed differences in age-specific HCC rates to differences in the age when the primary HBV encounter has occurred. There is a higher tendency for HBV infection to turn to chronic infection in pediatric or neonatal infection.[9] Ethnic variability in HCC is believed to be a reflection of differences in prevalence and acquisition time of the risk factors.[5] Progression from acute HBV liver infection to CHB occurs in around 90% of newborns who are infected perinatally, as opposed to 20%-30% of patients infected in early childhood and less than 5% of patients infected as adults.[12,13]

In children, PLC is not common, it only accounts for 0.5-2.0% of childhood cancers.[14] HCC is estimated to be 0.5-1.5 per 10^6 population.[14] These estimates were calculated based on two main large surveys that included children with liver cancer.[15,16] It is important to point out that HCC is not a common type of liver cancer among children younger than 4 years of age. The most predominant type in that age group is hepatoblastoma.[14,17] Different studies have identified HCC to be the most common type of PLC among children aged 10 years,[18] and adolescents aged 15 years and above,[19] accounting for 87% of PLCs.[17] Overall, the histological type varies remarkably over 5-24 age range.[17] HCC is considered one of the 10 most common cancers in adults globally, with a 2-3 times higher incidence in Sub-Saharan Africa and Eastern Asia.[14] Recent studies have also reported a shift in Africa to affect a younger age, the

pediatric age group.[14] Considering the established relationship between HBV carrier status and HCC in adults and its long latent period, it possible to conclude that it is difficult to obtain accurate measurements of the incidence of liver HCC among children at an early age. However, a study by Moore et al has concluded that the incidence of HCC progressing among children in South Africa, and it following the trends in adults. Those changes are appreciated in spite of the considerable logistic difficulties and resource limitations in detecting cases and collecting data.[14]

Epidemiology of Viral Hepatitis – Hepatitis B Virus (HBV)

Hepatitis B is considered a major health problem at a global scale and is the most common cause of viral hepatitis in the world.[13] It is also estimated that 70%-95% of the global population has been exposed to the virus.[12] According to the WHO, around 240 million people have chronic hepatitis B infection (CHB) today, and around 600,000 people die every year of acute or chronic complications of the HBV.[12]

HBV infection has different routes of transmission that vary regionally. In countries where HBV is endemic, the most common route of transmission is vertical transmission (from mother to child), and up to 90% of infected cases progress to develop chronic infections.[5,13] On the other hand, in countries where HBV is not as prevalent, the most common route of infection transmission is the horizontal transmission (sexual transmission), and over 90% of the infections resolve spontaneously.[5] Table (1) below provides a summary of the regional variations in hepatitis B epidemiology.

Table (1): Geographical variation in hepatitis B prevalence* and patterns of transmission.[12]

Pattern of prevalence	**Geographical area**	**Predominant age at infection**
High ≥ 8%	Southeast Asia, China, Pacific Islands, Sub- Saharan Africa	Perinatal and early childhood
Intermediate 2%-7%	Eastern Europe, the Mediterranean basin, Middle East, Central and South Asia, Japan, Central and South America	Early childhood/adolescence
Low < 2%	United States and Canada, Western Europe, Australia and New Zealand	Adult

** Prevalence of the hepatitis B surface antigen (HBsAg)*

The majority of acute HBV infections resolve naturally without treatment. However, an acute infection may progress into chronic disease.[13] Progression to CHB poses higher risk of death from liver-related diseases by 15-20%, including HCC development.[2,13]

Hepatitis B Vaccine (HepB Vaccine)

The HepB vaccine was first made available in 1982.[20] In 1991, the Global Advisory Group of the Expanded Programme of Immunization (EPI) called for all countries to include HepB vaccine in their vaccination programs.[21] In 1992, the World Health Organization (WHO) endorsed this recommendation and set a goal for all countries to incorporate hepB vaccine into national routine infant immunization programs by 1997[22], aiming at preventing 80% of new HBV infections by 2001.[21] By 1998, over 90

countries have included HB vaccine as routine antigen in their national programs. Those countries included about half of the world's children and about 70% of the world's carriers.[21]

The Global Alliance for Vaccines and Immunisations (GAVI), as private-public partnership was assembled to promote health and immunizations worldwide. GAVI represents WHO, UNICEF, United States Agency for International Development (USAID), World Bank, Bill and Melinda Gates Foundation, Rockefeller Foundation, technical agencies such as the CDC, ministries of health of less developed countries, and the pharmaceutical industry.[23] Today, GAVI provides technical assistance and funding, through the Global Fund for Children's Vaccines (GFCV), to 74 of the world's poorest countries to introduce new and underused vaccines into their routine infant immunization programs.[23]

The morbidity related to HBV infection is associated with the chronic infection in particular. The association between chronic infection and development of HCC has been clearly demonstrated in the literature.[6] Routine infant HepB vaccination with a 90% coverage starting at birth would prevent 84% of the death related to HBV infection around the globe,[3] and would prevent 85% to 95% of CHB infections.[6,21] HepB vaccination has also proven efficacious in reducing the vertical transmission of the virus (mother-to-infant transmission). The vertical transmission of the virus is of a particular significance because it is a major contributor to chronic HBV infection.[7] Many Asian countries with high rates of HCC have implemented neonatal HepB vaccination, and this has had an evident effect of declining HCC rates already,[5,7] For instance, in 1984, Taiwan became the first country to implement a national program for vaccinating newborns against HBV[10] and administer anti-HBV antibodies to infants born to high-risk mothers (positive for HBsAg) and to mothers who are HBeAg-positive.[2] Over the following years from 1986 onwards, the HBV vaccination program was scaled up to introduce the vaccine to preschool children, primary school children, middle-school children and adults, respectively.[10] This program has been remarkably successful in lowering the prevalence and mortality associated with HBV among children.[13] The HCC incidence in children aged 6-14 years has declined from 0.70 per 100,000 in 1981-1986 to 0.36 per 100,000 in 1990-1994.[7] This accounts for a 65%-75% reduction in HCC incidence.[2] Another study is the randomized field trials conducted in Qidong province in China.[24,25] This was a community-randomized, large-scale, controlled study of universal HepB vaccination of newborns in Qidong County of China, where there was high HCC incidence. The trial achieved 98% vaccination coverage among 35,798 children. The study concluded that there was a 84% reduction in mortality among the vaccinated group (HR= 0.16, 95% CI 0.03–0.77).[26] On the other hand, the Gambia has a high HCC incidence, endemic CHB and near ubiquitous AFB-1 exposure.[27] In 1986, the Gambia Hepatitis Intervention Study (GHIS) was initiated to assess the efficacy of HBV vaccination in the prevention of HCC.[27] The HepB vaccine was rolled out through cluster-randomized design.[28] The Gambia was the first African Country to establish a National Cancer Registry (NCR) with substantial rural coverage.[27] Data form that NCR indicated that HCC is the most common cancer among men and the second most common among women, and around 15% of adults are chronic HBsAg carriers and have acquired it through horizontal transmission during young childhood.[9] The GHIS demonstrated that HB vaccination when implemented at a national scale in a developing-country setting, such as in the Gambia, it is highly effective in the preventing HCC.[27]

It is particularly a necessity to prevent HBV acquisition among children. The majority of young children who contract HBV become asymptomatic carriers, potential sources of infection, and most importantly, have higher risks for developing HCC.[29] Individuals in high-risk countries become chronic carriers of the HBV in infancy or young childhood.[6] Therefore, this age group should be the target group

for vaccination programs, as vaccinating older populations would have little, if any, effect on decreasing the HBV carrier state prevalence.[6] Vaccination programs have focused on the newborns who bear higher burden of progression to chronicity than older children or adults, as explained earlier under the risk for developing HCC.[13]

GENERAL RESEARCH QUESTION

This study aims to evaluate the association between HepB vaccination coverage and the incidence of liver cancer at a global level. We focused on populations younger than 25 years of age considering that the earliest universal HepB vaccination programs have started between 20-30 years ago.

SPECIFIC RESEARCH QUESTIONS

- What is the global trend of liver cancer incidence in the under 25-years age group?
- What is the global trend of HepB vaccination coverage against HBV?
- Is there a possible causal relationship between HBV vaccination coverage and the liver cancer incidence in the under 25-years age group?

Conceptual Map

Figure (1) below illustrates a conceptual map that shows the etiology and different histopathological types and causes of liver cancer, and delineates the causal pathway that can be interrupted through HBV vaccination.

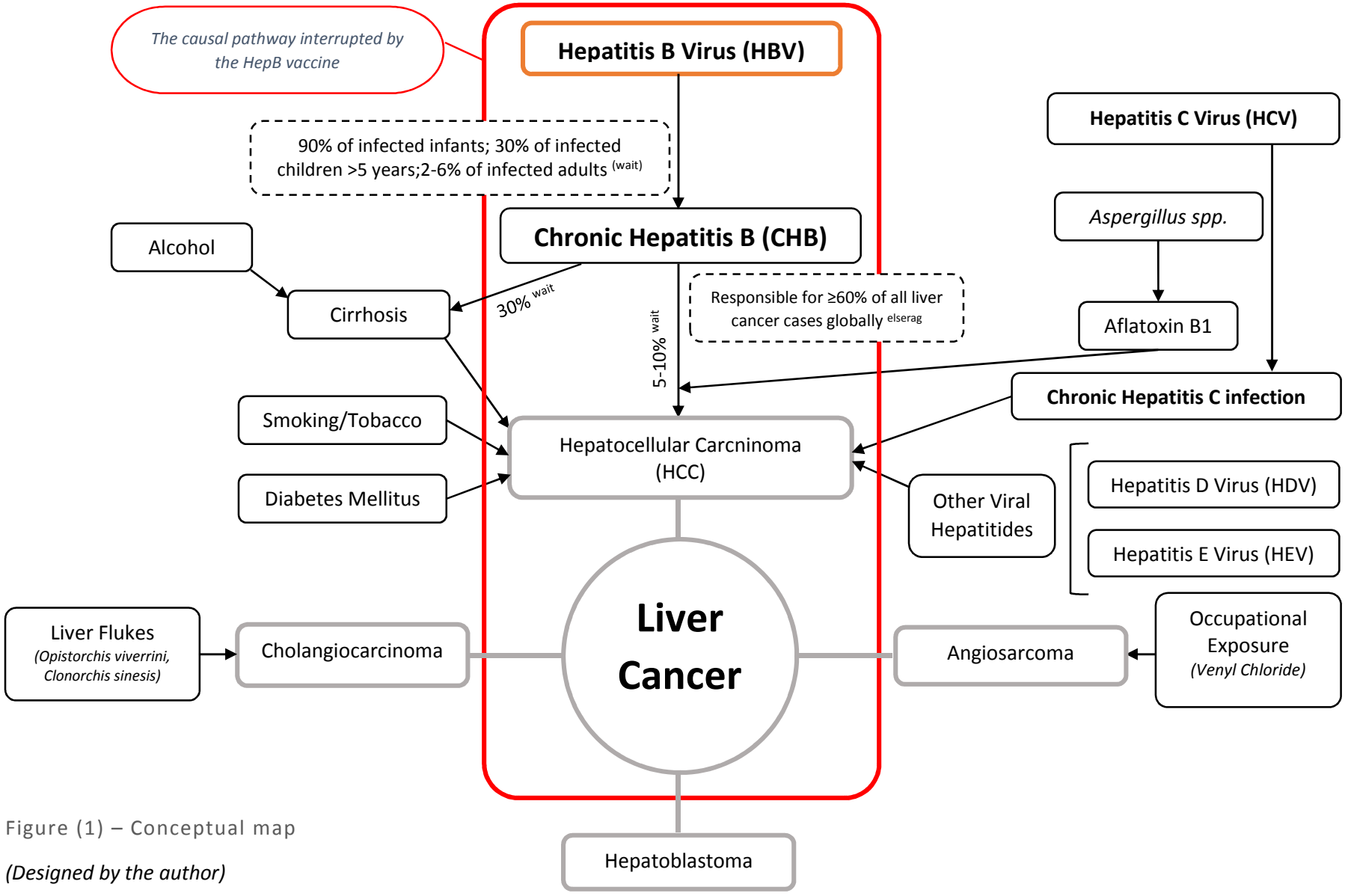

Figure (1) – Conceptual map

(Designed by the author)

METHODOLOGY

Study Type and Design

This is an analytical epidemiological study, that targets 5-year birth cohorts from 153 eligible countries. We included all cohorts from eligible countries. We decided that a country was eligible if data about HepB vaccination coverage as well as data on liver cancer incidence were available, over a period of 5 years at least from any year of starting implementing universal HepB vaccination before 2007. The different countries had different numbers of birth cohorts depending on when they implemented the universal hepB vaccination programs.

Analysis

Independent Variables

We used publically available data about HBV vaccine coverage from the WHO website.[30] The data were coverage rates for the triple-dose vaccine for 195 different countries. In order to standardize our data, we selected the data reported by the WHO, not the official data reported from every country. This is because the WHO has a standardized method to correct errors in reported vaccine coverages from the different countries.[31] Different countries started implementing and reporting on HBV coverage at different years. The earliest countries that started implementing the HBV started it in 1989.

According to the WHO, information about vaccinations are collected mainly through household surveys. The three main types are the Expanded Programme on Immunization (EPI) cluster survey; the UNICEF Multiple Indicators Cluster Survey (MICS); and the Demographic Health Survey (DHS), but among the three, EPI is the most feasible.[31] In June 2000, the WHO and UNICEF began a retrospective review of data on national immunization coverage rates over the period 1980-1999 through a WHO/UNICEF Joint Report Form (JRF) on Immunization. They used those data to estimate the most likely levels of immunization coverage.[31]

Dependent Variables

The dependent variables in this study are the numbers of cancer cases disaggregated by age group per year per country. We were able to calculate the incidence rate using these incidence data as well as the respective total population for each age group. We used those two indicators to calculate the total incidence rates per 100,000 population. Whenever available, we used reported liver cancer incidence from cancer registry data and death registry data. For countries with missing or sparse data, other covariates were used to estimate cancer incidence, incident cases and respective populations. Box (2) below lists the covariates used in estimating the incidence of liver cancer. Those estimates were used in the Global Burden of Disease study by the Institute of Health Metrics and Evaluation (IHME).[32] We had estimates of the general incidence of liver cancer for each age group.

Box (2) – Covariates in the estimation of liver cancer incidence for the GBD study, IHME

Alcohol	Animal fats	Education
HBV seroprevalence	BMI	Red meat consumption
HCV seroprevalence	DM	Tobacco
Liver fluke endimicity	Health system access	Lagged- distributed income (LDI)

The IHME data were for the years 1980 – 2013, for 5-year-age groups starting from 5-9 years up to over 90 years old. In order to obtain incidence from the data set that we have, we calculated the incidence rates for the different age groups (we combined the number of cases per gender per year across all age groups and divided the total by the respective total population).

Data Cleansing

After matching countries from the two data sets, and applying our inclusion criteria, we narrowed our country list down to 153 countries. Since the earliest data available on HBV vaccine coverage were from the year 1989, we could only look at age groups <25 years. We specifically looked at the age groups 5-9 years, 10-14 years, 15-19 years, and 20-24.

On the other hand, data on HBV vaccine coverage were for single years and for less than 1 year-old children. Therefore, we created five-year groups for HBV vaccine coverage starting from 1989 and ending in 2010. For every five years of vaccination, we identified the mid-interval year to represent the respective interval. For example, for the years 1990 to 1994 of HBV vaccination we selected year 1992 to represent the interval. We calculated the median HBV vaccination coverage for every interval and matched it with cancer incidence rates for the different age groups, 5 years, 10 years, 15 years and 20 years later. In this way, we were able to study the different birth cohorts (aged 5-9, 10-14, 15-19, and 20-24) and examine the relationship between vaccine coverage and liver cancer incidence across the different birth cohorts in the different countries.

Missing Data Analysis

Vaccination coverage data included missing observations from different countries after they have started their universal vaccination programs. Overall, after combining data about the different birth cohorts from the different 153 countries that we included in the study, we had a total of 2257 observations across the different birth cohorts born between the years 1989 and 2006. As explained earlier, data are grouped into cohorts born in 5 consequent years. Whenever data are missing for more than 2 of the 5 years, we count this as a missing median vaccination coverage data for respective birth cohort and omitted it from the analysis. This is also known as “pair-wise deletion” and it is the most commonly used method for missing data analysis.[33] Overall, there was a total of 128 missing observations from the vaccination coverage across the different birth cohorts, accounting for 5.67% missing data of the total data set. We could not conclude a specific pattern for the missingness. Therefore, we made the assumption that missing data mechanism (MDM) for those 128 observations is missing completely at random (MCAR). We therefore, chose to conduct a complete case analysis of the available observations.

The Study Hypothesis:

This was a confirmatory statistical analysis. In the way we organized our data, we looked at every birth cohort independently. For illustration, A birth cohort that was born in the period 1990-1994 will be aged 0-4. We considered this cohort to have received the vaccination. We started exmining the liver cancer incidence rate in this cohort when it became a 5-9 year-old age group in 1997, and we examined the same cohort in 2002, but as a 10-14 age group this time, and so on. In this way, we knew that our observation were not independent and we saw high correlation in the median vaccination coverage observation (-0.934). We used a mixed-effects poisson regression model for our analysis. We ran this model through the Generalized Linear Latent And Mixed Model (GLLAMM) package in Stata 13. Our outcome variable was the cancer cases, and our predictor variable of interest was the median

vaccination coverage, adjusted for the year of observation, age group (as continuous variable) as fixed effects. We controlled for our latent variable in the model was the countries as a random effect. We had the population as an offset. Our model follows the statistical formula below:

$$\mathbb{E}[cancer\ incidence|HBV\ vaccination\ coverage, Year, Age\ Group] = \alpha + \beta_{vaccination\ coverage\ \%} + \beta_{Year} + \beta_{Age\ Group}, random\ effects(countries), offset\ (population)$$

RESULTS

Descriptive analysis:

Our study included 2129 observations from 153 countries. We included median HepB vaccination coverage data from the period between 1991 and 2008. We also included estimates for liver cancer incidence from the period between 1996 and 2013. The 5-year median HepB vaccination coverage ranged between 1% and 99%. We only examined the 4 age groups indicated earlier. Table (2) summarizes these findings.

Table (2) – Descriptive statistics of the study variables

Variable	Min.	1st quantile	Median	Mean	3rd quantile	Max.
Median HepB coverage	1%	78%	90%	82%	96%	99%
Cases	0.0	0.0	0.4	3.3	1.7	219.6
Population	3,721	8,666	516,280	2,713,000	2,606,043	122,000,000
Incidence *Per 100000*	0.0	0.04	0.07	0.12	0.11	8.33

Table (3) below demonstrates the breakdown of the birth cohorts that were included in the study. Following our analysis approach, there were only 29 birth cohorts that were born in the period 1989-1993. Those 29 birth cohorts were from 19 countries that have started the universal vaccination program in that same period. This is why we have a relatively small number of cohorts aged 20-24 in our study. On the other extreme, we have a total of 2129 birth cohorts from the four different age groups (5-9, 10-14, 15-19, 20-24) who were born in the study period 1989-2008, and from all 153 countries.

Table (3) – Descriptive statistics of study observations

Age group	Latest year of starting universal HBV vaccination coverage	Year interval where the cohort was born	# of cohorts studied	Cumulative # of cohorts	Cumulative # of countries
20-24	1993	1989-1993	29	29	19
15-19	1998	1989-1998	214	243	51
10-14	2003	1989-2003	598	841	103
5-9	2008	1989-2008	1288	2129	153

Bivariate Analysis

We examined the trends of vaccination coverage over the years 1989-2013, where data were available [figure (2)]. Each point represents the HepB vaccine coverage rate for one country at the respective year in the X axis. We also examined the trend of liver cancer incidence rates over the years 1980-2013 for populations younger than 25 years [figure (3)]. Each point represents the liver cancer incidence for every age group from one country at the respective year in the X axis. We found an overall increasing vaccination coverage trend and that most countries have reached high hepB vaccination coverage rates. There was less spread of vaccine coverage rates towards the recent years. With regards to the liver cancer incidence trends, there was no particular trend that was evident visually. The overall trend of liver cancer across the different age groups was steady over the years 1980-2013.

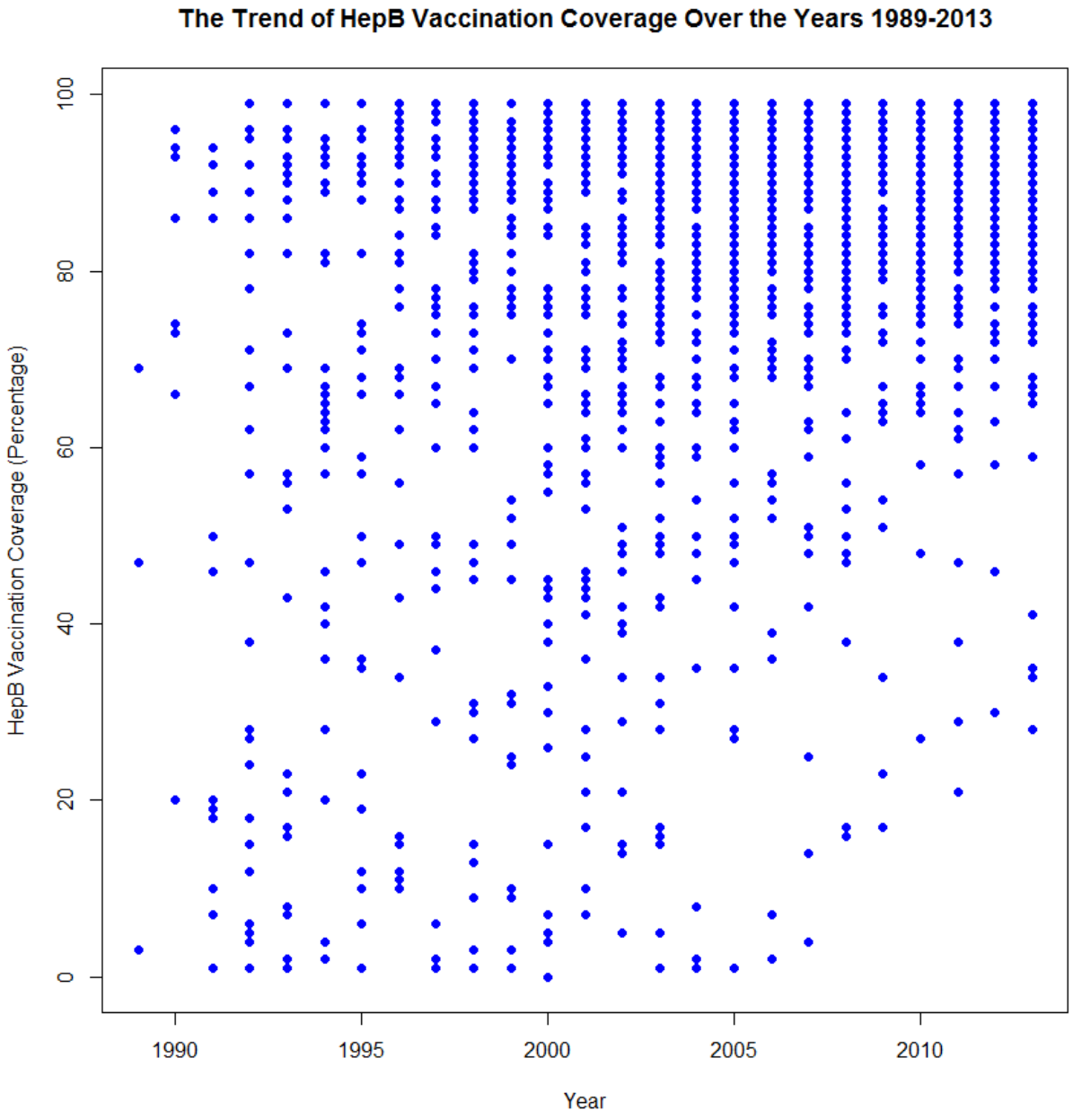

Figure (2) – The trend of HepB vaccination coverage

Figure (3) – A scatterplot of liver cancer incidence in the different birth cohorts vs. the year of vaccination of the respective cohorts

Using our analysis model, we found higher HepB vaccine coverage rates were associated with lower liver cancer incidence rates (p-value = 0.003). We estimate that among populations aged 5-24 years, higher 5-year median vaccination coverage rates by 10% were associated with a relative risk that is lower by a factor of 0.948 cancer incidence after adjusting for age group and year of observation (95% CI: 0.916, 0.982). Graph (4) below shows the scatterplot of liver cancer incidence vs. the median HBV vaccine coverage. Each point represents the liver cancer incidence rate for one country with the respective HepB vaccination coverage rate on the X axis. The liver cancer incidence on the Y axis is presented in a logged scale because the liver cancer incidence rates are very low across the study population. The logged scale helps emphasize the spread of observations, and demonstrate the trend of the association.

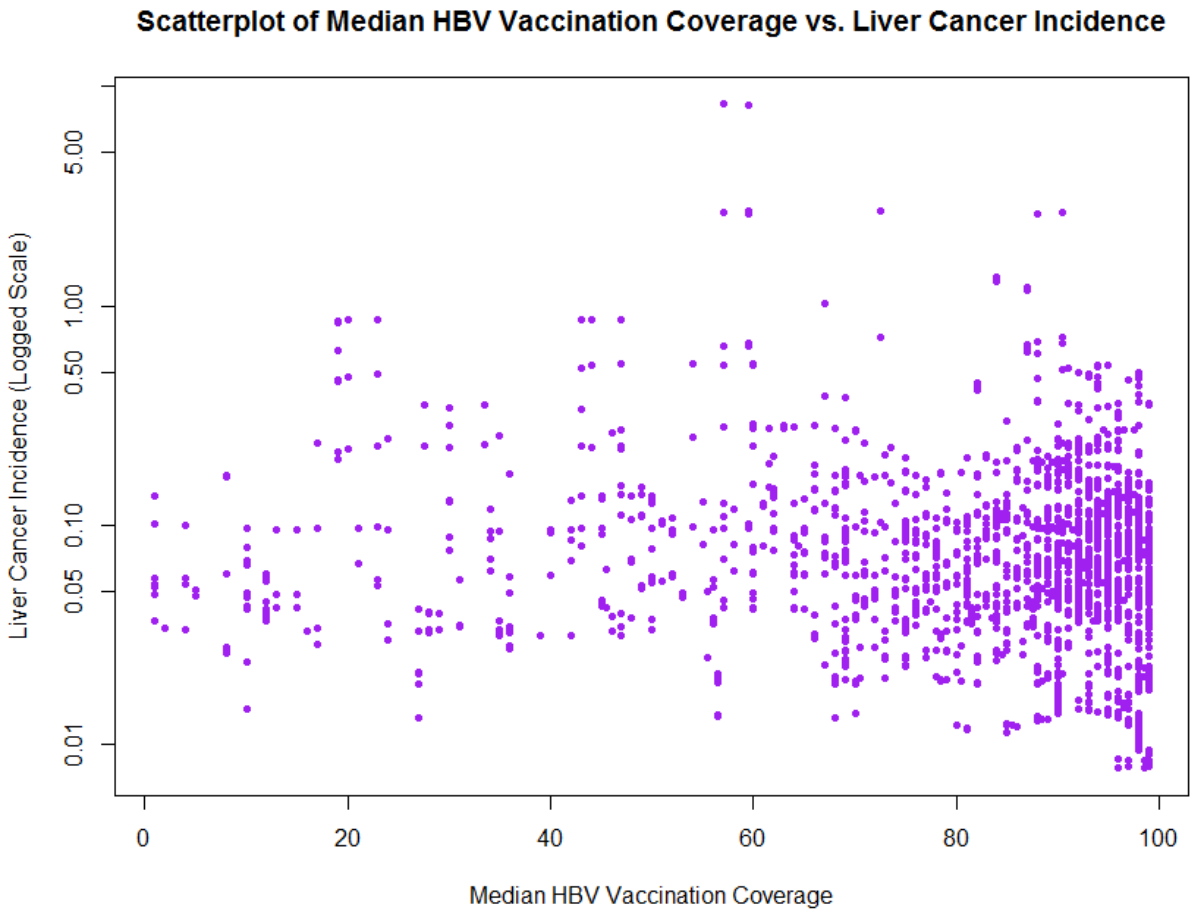

Figure (4) – A scatterplot of liver cancer incidence vs. the vaccination coverage

DISCUSSION

According to our results, HCC incidence was inversely proportional to HepB vaccine coverage. The overall trend of HepB vaccination coverage has been clearly increasing as many countries have reached high levels of coverage (>90%). However, those are the national coverage rates, and they do not necessarily reflect different parts of the different countries, where access to basic health services such as vaccination is limited. The liver cancer incidence rates (graph 3) does not show a specific trend over the years across the different age groups. This is most likely because the disease is rare among the studied populations and it would be difficult to show the trend in them. In spite of that, our model showed that there was a statistically significant reduction.

Liver cancer is considered a disease of the elderly. The peak incidence is in the sixth decade of life.[10,11] Therefore, it may need around 40 more years to witness the actual impact of the universal HBV vaccination and prevention efforts on HCC incidence. This explains the paucity of trials to demonstrate this impact. However, the disease is witnessed among children, adolescents and adults in countries with high burden of HBV (or CHB, more specifically). Therefore, it might be possible to demonstrate the impact of HepB vaccination on HCC incidence.[11] The rates of HCC among younger population groups in those countries can be an early indicator of the how effective the HBV vaccination in reducing the rates of liver cancer. To our knowledge, this is the first study to address the association between HBV vaccination coverage and liver cancer incidence at a global level. Other studies were only done in the Gambia,[3,9,27,28,34] Taiwan,[10,11,21,23,26,34] Thailand, and Qidong county in China.[24,25,34]

Limitations of Our Study

We acknowledge a number of major limitations in our study. The first was the fact that we did not have a breakdown to specific estimates for the different histopathological types of the disease. Different references reported different estimates of HCC among the population between the ages 5-24. Different studies reported different ages of predominance of hepatoblastomas over HCC. Different studies have reported that hepatoblastoma are the most predominant histopathological type of liver cancer among children up to 4 years of age,[14,17] 10 years,[18] and 15 years of age.[19] There are also different patterns that vary over 5-24 age range.[17] These different estimates limited our estimation accuracy of the HCC, the liver cancer histopathology of interest in our study. If we were able to collect more accurate data on HCC diagnosis, our results would have been more robust. With regards to the vaccination coverage data, the reported figures from the different countries are not necessarily homogeneous at the subnational levels. One would expect disparities across subnational estimates, and across different socio-demographic groups.[31]

The other limitation is what identified in the field of epidemiology as the “ecologic fallacy”.[35] Ecological fallacies are perceived as crude attempts to infer correlations from group data to individual-level data.[36] We argue that such studies even when studying individual-level associations, group-level data are crucial in defining the public health problems that need to be addressed.[37] The different risk factors that we have identified in the literature review earlier in this study have come to our knowledge through population-level studies.[37] Besides, it is increasingly being recognized that some risk factors for disease, although individual, operate at population level and cause disease as determinants of exposure for the individual. In our study, we identified HBV vaccination coverage at a population level as determinant of the individual level of CHB status. We believe that, on the contrary, failure to account for the importance of population context in disease association with risk factors could be identified as

"individualistic fallacy",[37] where the focus only shed on individual characteristics and the population-level characteristics are ignored.

A third limitation is that our study does not account for the fact that different countries/regions of the world have varying patterns of primary etiologic factors.[27] Different projects have identified that the different causes of HCC have independent and combined effects.[27] Our study has put that into consideration. The natural history of HBV infection differs in different population and the different studies conducted in The Gambia, China and Taiwan reflect varying prevalence of HBsAg among vaccinated populations in the different setting.[3] This reality has direct relevance on the implementation of HepB vaccination strategies globally.

Finally, we did not account for the impact of CHB treatment on HCC incidence. Neither did we account for the preventive effect of HepB immunoglobulins (or intravenous immunoglobulins "HBIGs") that were particularly given to high-risk infants born to HBsAg mothers.[34,38] This was a strategy known as "high-risk vaccination strategy", and it was an active part of the health policy before universal HepB vaccination was implemented adopted for controlling HBV in countries with low HBV endemicity.[34,39]

Strengths of Our Study

In spite of the limitations we presented, our study has the advantage as being the first to measure the association between HepB vaccination coverage and liver cancer incidence at a global level. These results support the results that we have found from the other studies, mainly the ones conducted in The Gambia, Taiwan and China, as mentioned previously. The GLLAMM model that we used in our analysis, allowed to control for the differences in countries as random effects.

Implications for: Theory, Practice, Research

Data from countries endemic with HBV and liver cancer (HCC in particular) are not necessarily representative of the global status, since the epidemiologic profile differs globally (table 1). The models used by the IHME for estimating liver cancer incidence can be further improved and made more specific to the histological diagnoses. We reflected in our project how the histopathology of liver cancer changes over the different age groups and also across the different parts of the world. Therefore, histopathological diagnosis is needed for case ascertainment and accurate measurement of the effect size, being the association between liver cancer incidence and HepB vaccine coverage in this study. Finally, we recommend that future studies acknowledge the impact of HepB vaccine on the chronic HBV status and HBV-carrier status as an intermediate step before assessing the impact on HCC directly. As the conceptual model reflected, this was not a simple pathway.

CONCLUSION

Finally, we conclude that, at a global population level, higher HBV vaccination coverage is associated with reduced liver cancer incidence rates among age groups younger than 25 years old. Future analysis with growing data on vaccination coverage and more accurate cancer registry data are warranted.

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