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Presentation

Population-Based Interventions to Reduce the Public Health Burden Related with Hepatitis B Virus Infection in The Gambia, West Africa

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Abstract: In The Gambia, West Africa, the prevalence of chronic hepatitis B virus (HBV) infection in adults exceeds eight percent and hepatocellular carcinoma (HCC) has been the most frequent type of malignancy. Two population-based intervention studies to control HBV infection, namely, GHIS (Gambia Hepatitis Intervention Study) and PROLIFICA (Prevention of Liver Fibrosis and Cancer in Africa), are discussed. The GHIS started in 1986 as a nation-wide trial of the HBV vaccine to evaluate the effectiveness of infant HBV vaccination in preventing HCC in adulthood. The vaccine was progressively introduced into the Expanded Program of Immunization (EPI) of The Gambia over four years in a phased manner, called the “stepped-wedge” design. This was because instantaneous universal vaccination in the country was impossible for logistic and financial reasons. However, this design also allowed the study to have an unvaccinated control group which consisted of the newborns of the areas where HBV vaccine has not yet been incorporated in the EPI. To assess the outcome, a national cancer registry was founded and all HCC patients in this birth cohort are linked with the vaccine trial database. The study is still ongoing to answer whether the HBV vaccine in infancy prevent HCC in adulthood in The Gambia.

Although the universal HBV vaccination since 1990 has been successful in reducing the prevalence of chronic HBV infection in young Gambians, the number of HCC cases may not decline over the next decades as people infected prior to the immunization program are likely to continue to develop the diseases. To reduce the HCC incidence through community-based screening of HBV infection and provision of antiviral therapy, the PROLIFICA project started in 2011. Study hypothesis and design of these two studies, GHIS and PROLIFICA, are further discussed.

Key words: Hepatitis B, carcinoma, hepatocellular, hepatitis B vaccines, antiviral agents, public health, epidemiology, The Gambia, Africa

INTRODUCTION

The Gambia is the smallest country in the African continent with a population of 1.73 million people. The UK Medical Research Council (MRC) established its branch in The Gambia in 1947. Since that time, the MRC Gambia has been producing numerous important studies, which hugely influenced the global public health. My presentation will focus on study hypotheses and designs of two population-based intervention studies to control hepatitis B virus (HBV) infection in The Gambia, namely

GHIS and PROLIFICA. The GHIS stands for the Gambia Hepatitis Intervention Study, which is a hepatitis B vaccine field trial started in 1986. The project was originally funded by the Gambian government, WHO-IARC (International Agency for Research on Cancer), Italian Government and MRC. The second study, PROLIFICA stands for Prevention of Liver Fibrosis and Cancer in Africa. This is to treat chronic hepatitis B carriers with antiviral treatment and started in 2011. The study is funded by the European Union, MRC and Imperial College London. As I am working within PROLIFICA but not in

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the GHIS, my talk on GHIS is based on the historical literatures that I read.

GHIS (GAMBIA HEPATITIS INTERVENTION STUDY)

Background

When the GHIS was prepared in the early 1980's, there had been accumulating evidence that there is etiological association between HBV infection and hepatocellular carcinoma (HCC) [1]. It was also well known that sub-Saharan Africa (SSA) is highly endemic for HBV infection and most of transmission occurs during childhood rather than perinatal mother-to-infant transmission [2]. As a prevention, plasma-derived hepatitis B vaccine was already shown to be effective against acute and chronic HBV infection [3]. However, there were two important questions: how long the immunity lasts after the vaccine and whether the vaccine can prevent HCC, which is the most important complication of chronic HBV infection [4].

There was a dilemma among public health experts about the use of hepatitis B vaccine in SSA: whether to immediately start mass vaccination campaigns in SSA or to conduct randomized controlled trials before such programs to have direct evidence that the vaccine prevents HCC [4]. Both strategies have pros and cons. Mass vaccination would be challenging because the cost of the vaccine was still high and the availability of vaccine was limited at that time. In contrast, randomized controlled trial would present ethical problems because this study design creates a group of people who do not receive the vaccine, which was already proven to be at least effective against chronic carriage of infection. Moreover, randomizing children at an individual level would pose logistic challenges given the planned size of the study.

After considering these, the GHIS finally started in an attempt to evaluate the protective effectiveness of infant hepatitis B vaccination on the incidence of HCC in adulthood. The vaccine was incorporated into the existing EPI (Expanded Program of Immunization) program in The Gambia without adding any new additional schedule, at birth and month 2, 4, and 9 (Fig. 1).

Hepatitis B vaccine trial

The design of this study was called "stepped wedge design" (Fig. 2) [4]. As instantaneous introduction of nation-wide hepatitis B vaccine was impossible at that time due to financial and logistic constraint, it was decided to introduce the vaccine in a phased manner on a group by group basis until the entire population is covered. The Gambia was covered by 17 EPI teams, and one of the 17 teams was randomly selected as the first team to start inte-

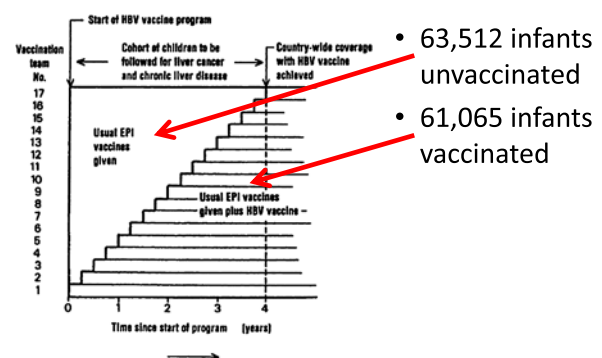
GHIS – Objective –

- To evaluate the protective effectiveness of **infant** HBV vaccination on the incidence of HCC in **adulthood**

Age (month)	Vaccine
Birth	BCG, polio 1, HB 1
2	DPT 1, polio 2, HB 2
3	DPT 2, polio 3
4	DPT3, polio 4, HB 3
9	Measles, yellow fever, HB 4

Fig. 1. The objective and immunization schedules of the GHIS.

Stepped wedge design



Hall et al., 1987

Fig. 2. Study design of the GHIS.

grating the hepatitis B vaccine in the program. Since July 1986, all children born in the area covered by the first EPI team were given hepatitis B vaccine, while other children who were born in other areas became the unvaccinated controls. Three months later, the second area that had been randomly selected started providing hepatitis B vaccine. Then, all newborns in the first and second areas received the vaccine, whereas those born in other areas did not. It was four years after the first team had started that the whole country was covered with hepatitis B vaccine. This progressive introduction of vaccine between 1986 and 1990 resulted in 61,000 vaccinated and 63,000 unvaccinated newborns [5]. Without compromising the ethical issue, the GHIS could have an unvaccinated control group. Of note, the statistical power of this approach is > 70% of that of a simple randomization in which one-half of the EPI teams are allocated to give hepatitis B vaccine.

Measuring the outcome

Next was to measure the outcome, which is HCC. HCC does not occur 1 or 2 years after the infection; it usually takes decades to develop. In 1986, GHIS established The Gambia National Cancer Registry in order to capture all the incident cases of cancer within the country [6]. Whenever a staff in the Registry is notified of a new cancer case, both the clinical and demographic information such as name, sex, year of birth, birthplace and name of parents were collected. The demographic information of the HCC patients who were born in The Gambia between 1986 and 1990 will be linked with information kept in the vaccination database, allowing identification of the vaccination status of the individual (Fig. 3). The site of BCG scar would also help to distinguish whether or not the person received the hepatitis B vaccine. BCG had been given on the left forearm in the hepatitis B vaccination group and on the right in the control group. In addition, foot and palm prints that were taken when the child entered the study will be compared with foot and palm prints of the HCC patients for linkage [4].

How long will it take to have final results? In order to calculate this, several assumptions were required (Fig. 4). These include vaccine coverage, hepatitis B vaccine efficacy against chronic infection, impact of perinatal infection, which is a major cause of vaccine failure, and proportion of HCC attributable to HBV infection [5]. It was estimated that this would take 30 to 35 years, so within a few years this public health question may be answered. However, the study naturally produced many intermediate endpoints before reaching this final result. One of them is, for example, vaccine efficacy against chronic carriage after 20 years was 94% [7]. This suggested that booster vaccines may not be necessary at least until that age. And more importantly, the study could show that

the introduction of hepatitis B vaccination into the EPI was feasible in an African country [8].

PROLIFICA (PREVENTION OF LIVER FIBROSIS AND CANCER IN AFRICA)

Background

Thanks to GHIS and other vaccine trials in 1980's, feasibility of the HBV vaccination program and its effectiveness against chronic infection was well established. In The Gambia, national infant hepatitis B vaccination program replaced the GHIS when the vaccine trial finished in 1990. Meanwhile, the price of hepatitis B vaccine dramatically reduced. Based on these, in 1992, WHO recommended all member states to include hepatitis B vaccine as a universal vaccination by 1997. By the end of 2012, 181 countries adopted this [9]. However, widespread use of this effective vaccine gave a false impression that HBV infection is no longer an important public health problem. Indeed, one of the Millennium Development Goals is specific for infectious diseases and this only includes HIV, malaria, and tuberculosis. Other tropical infectious diseases formed the group called tropical neglected disease, but viral hepatitis is not included. There seems to be no place for viral hepatitis in the global health agenda [10].

However, the health burden associated with HBV infection is still substantial. In 2005, prevalence of HBV infection in adults still remains high in SSA exceeding 8% in some countries [11]. Global burden of disease and injury study [12] estimated that out of 235 causes of deaths, liver cirrhosis ranked at 12th and liver cancer ranked at 16th in 2010. HBV infection ranked at 15th. These figures reflect that even though hepatitis B vaccination programs were

How to measure the outcome (HCC)??

- Established the **Gambia National Cancer Registry** in 1986 (Bah et al., 1990)
- Linking HCC patients with vaccination database
 - Name
 - Sex
 - Year of birth
 - Birth place
 - Names of parents
 - BCG scar
 - Foot & palm prints



Fig. 3. Outcome measurement in the GHIS.

How long will it take? = Sample size calculation

- Assumptions
 - Vaccine coverage
 - HB vaccine efficacy against chronic HBV infection
 - Impact of perinatal infection
 - Proportion of HCC attributable to HBV



It will take 30-35 years (in 2017??) (Viviani et al., 2008)

Fig. 4. Assumptions needed for the sample size calculation in the GHIS.

included in many countries, the people who had been infected before the introduction of the vaccination programs continue to suffer from carriage of HBV infection and also HCC [13]. We will probably see an increasing number of HCC patients over the next five to six decades in countries where HBV is endemic [14]. Then, do we just wait until they die without taking any action? Of course, not. We must consider treating chronic HBV carriers to prevent premature deaths from HCC. However, the access to HBV treatment is still largely limited in high endemic countries which are often resource-limited.

Before starting treatment for chronic HBV carriers in SSA, there are several questions to answer. Is there any effective treatment? Yes, there are good medicines called nucleos(t)ide analogues, which can be taken orally and are very effective in reducing the amount of virus [13]. It is different from 15 years ago when only interferon was available, which caused many side effects and was not effective in all patients. Are nucleos(t)ide analogues expensive? No; the Global Fund generic price of tenofovir, a nucleos(t)ide analogue, is less than ¥10,000 (100 USD) per year. Don't you need a liver biopsy and histopathologist to select a patient who needs treatment? Yes, assessing the degree of liver fibrosis is important for the treatment initiation, however, now there are alternative noninvasive methods to measure liver fibrosis [15]. Then, the last question is: how can you deliver the care and treatment? We can just learn from the HIV program. However, unfortunately, there is still ongoing discrimination regarding access to antiviral therapy. For example tenofovir, which is effective for both HIV and HBV, has been freely available in some African countries. However, some donors still refuse to use this drug for HBV mono-infected patients [16].

Study design

It was in such a context that PROLIFICA started in 2011 in The Gambia and Senegal. The primary objective is to assess whether antiviral therapy using tenofovir reduces the incidence of HCC in West Africa. Another objective is to determine applicability and effectiveness of population-based screening, clinical assessment and treatment in West Africa.

Before treating someone, we have to identify chronic carriers of HBV. For example, antenatal care or blood banks would be easy places to find chronic carriers. However, we have been conducting a community-based screening, because our target is the general population in The Gambia. This is the original plan (Fig. 5). Our aim is to have 5,500 people for the screening. Assuming the prevalence of HBV infection is 15%, we will have 825 people

who carry the virus. They are all invited to the liver clinic for further investigation. Chronic HBV carriers who meet the treatment criteria of international guidelines (EASL (European Association for the Study of the Liver) guidelines) are treated with tenofovir, while those who do not meet treatment criteria are followed without antiviral therapy for 5 years. Because tenofovir was already proven to be effective for chronic HBV infection, a clinical trial having a control group was considered unethical. The incidence rates of HCC in the treatment and observation groups will be compared with historical data from the Gambia National Cancer Registry. Together with Senegal, we estimated to have 300 carriers eligible for tenofovir. At this sample size, the study will have 71% power to detect a treatment efficacy of 60% at the 5% level of statistical significance over three years.

Community-based screening

We targeted the Western region of the country (Fig. 6) and because the distribution of other risk factors for HCC, such as consumption of crops contaminated by aflatoxin, was thought to differ between urban and rural areas [17], we stratified the area. Out of 1,450 enumeration areas defined by the Gambia Government for census purpose, we randomly selected 40 urban and 40 rural areas.

PROLIFICA in The Gambia

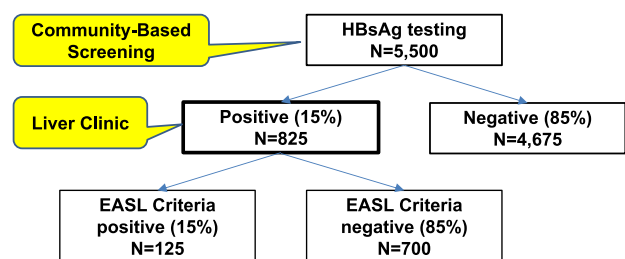


Fig. 5. Recruitment plan of the PROLIFICA.

Map of The Gambia

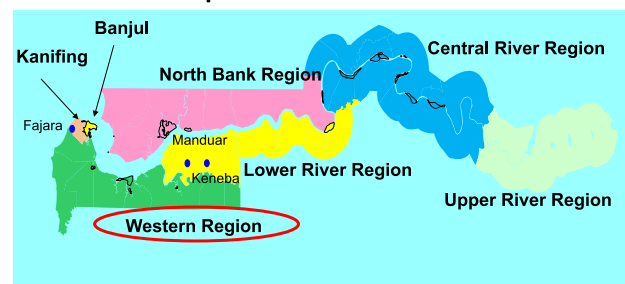


Fig. 6. Map of The Gambia showing the Western Region.



Fig. 7. Flow of procedures in the community-based screening.

All people over 30 years old who live in those selected areas are eligible. We set 30 years old as a cutoff because those less than 30 years are likely to have been vaccinated with hepatitis B vaccine.

In each area, we start by visiting the head of village to explain the purpose of the screening (Fig. 7). Then, once the approval from the head of village is obtained, we organize the community meeting. We bring the poster and leaflets and explain about our project to the villagers. After the meeting, we register all eligible persons who are living in the area. Then, we set up a screening point at the center of the village such as mosque or health center. After informed consent, screening for HBV infection is performed using point-of-care test, which gives us a result within 15 minutes. We do post-test counseling on site and those who tested positive are invited to the liver clinic usually one week later. At the liver clinic at the MRC Gambia we perform clinical examinations including abdominal ultrasound and Fibroscan, which is a noninvasive method to measure the liver fibrosis. Blood is collected and tested for hematology, biochemistry, HBV markers, HBV DNA and other viral co-infections. All the information necessary to assess patients' eligibility for the antiviral treatment are collected.

Future of the study

Some patients under the treatment may clear the infection before the study ends, and we may be able to stop the treatment. However, substantial number of patients may require life-long treatment. At the end of the study, we expect that the treatment program continues for the study participants either through raising new funds for further study or through integrating the program into the national healthcare system.

CONCLUSIONS

The GHIS and PROLIFICA are good examples of population-based field intervention studies in resource-poor settings. These pragmatic studies are set to determine how best interventions can be applied in populations and what impact they have in improving the people's health under the circumstances of general use. To conduct such a study, there are several requirements. First, a detailed study planning is imperative. This includes all aspects of an investigation, from formulation of specific study questions which determine the study objectives, through preparation for logistics, collection of data and its analysis, to dissemination of results [18]. Evidence derived from well planned field trials can guide public health policy, as demonstrated by GHIS. Second, the study design needs to be locally adapted, and consider fully the ethical implications. Third, it is important to involve researchers from a wide range of disciplines in designing and conduct of the study: from molecular biologists to medical anthropologists. Finally, the study needs to be "population-based" and study participants must be representative of the population. At the end of the study, the investigators expect the project to be integrated into the national public health system as mass vaccination or mass screening programs, and these will be for the entire population. We are not interested in subsets of people who can afford to come to medical facilities.

QUESTIONS AND DISCUSSION

Tetsu Yamashiro Thank you Dr. Shimakawa. You presented very interesting projects to us. The first one, over 30 years of cohort study, I really appreciate the investigators who started this project, foreseeing what would happen in the next 30 years. In the second one, PROLIFICA, how long the cohort will be followed?

Yusuke Shimakawa Five years.

Tetsu Yamashiro Endpoints seem to be more or less similar between GHIS and PROLIFICA.

Yusuke Shimakawa Yes, exactly. PROLIFICA is working together with the Gambia National Cancer Registry to strengthen the diagnostic capacity for liver cancer cases.

Tetsu Yamashiro Right, the other question I would like to address is that approaching the community in Africa is quite different from the way you approach the community in Vietnam or in the Philippines. To invite the people in the community to the screening, I guess you have got an approval from the government health committee, but was that enough?

Yusuke Shimakawa First, PROLIFICA is jointly organized with the Gambia Government and the ethics committee also includes the officials from the Government. But as you indicated, this is not enough in The Gambia. I imagine that in Vietnam the way to approach the community may be straightforward within the Socialist system, once the approval from the Government is obtained. In The Gambia, there are several key persons in a village and it is difficult to know who we should contact first to obtain a community approval. For example, in some villages we had successful screenings by contacting the head of village who was well respected by all the villagers. But in some villages where the head of village was absent or not functioning well, we had to contact a councilor who lives in the areas. Consequently, villagers who do not support the councilor for political reason did not attend the screening. Achieving high attendance to screenings is not always easy.

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