Global Control of Primary Hepatocellular Carcinoma with Hepatitis B Vaccine: The Contributions of Research in Taiwan

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Health workers and epidemiologists concerned with the prevention of cancer are largely unaware of one of the most significant recent developments in global cancer control, the integration of HBsAg vaccine into the national immunization programs in developing countries, including the poorest. PHC caused by chronic HB infection is the number one or two cause of cancer death in men in most Asian and sub-Saharan African countries and an important cause of cancer death in women. Chronic HB infection is approximately 90% preventable with proper use of HB vaccine but, until recently, this vaccine has been beyond the budgets of governments in the poorest countries; donors who supplied older vaccines were unwilling to pay for HB vaccine. In addition to the financial constraints, delivery services in the poorest countries were unable to access large parts of their populations with any vaccines.

Both of these impediments are being overcome by the creation, in the last 3 years, of GAVI and The Vaccine Fund. It is believed that the comprehensive use of HB vaccine will prevent about 1,000,000 deaths per year from PHC and cirrhosis of the liver (each year) in future birth cohorts. There has already been a significant impact on the prevalence of chronic HB infection in immunized birth cohorts in more than 135 countries, including China, southeast Asia, and sub-Saharan Africa where most PHC occurs.

The report in this journal, measuring the decline in PHC after immunization in Taiwan, is the latest in a remarkable series of studies in Taiwan dating back to the 1970s, in which much of the epidemiology of chronic HB infection, its link to cancer, and its prevention with HB vaccine were worked out. Before these studies, many researchers thought that aflatoxin from moldy groundnuts (peanuts) was the primary etiologic agent for PHC in developing countries. Whereas aflatoxin may be a cofactor in some countries, the Taiwanese studies showed that chronic HB infection is a necessary and sufficient cause of PHC, and that HB vaccine can prevent the development of chronic infection, strongly suggesting that routine HB immunization would be sufficient to prevent most PHC on a global basis (1).

In one of the most important epidemiological studies of the 20th century, Beasley et al. (2) followed 22,000 male Taiwanese health workers for more than a decade with almost complete follow-up. Rates of PHC were approximately 100 times higher among men who were HBsAg positive (495 per 100,000 per year) than among those who were HBsAg negative (5 per 100,000 per year). The validity of this association has now been confirmed in dozens of other studies; these are well reviewed in a monograph published by the IARC (3), which also discussed other confirmatory lines of evidence based on DNA integration and liver cancer in animals chronically infected with related hepadnaviruses.

It is now generally accepted that prevention of the HB-carrier state with HB vaccine will prevent PHC, and the global immunization strategy is based on this assumption. In the early 1980s, a major study in The Gambia was designed to measure directly the reduction in PHC in immunized cohorts, a task that many believed would take about 25 years. Using an innovative and controversial step-wedge design, most Gambian newborns were recruited into the study over a period of 4 years in a way that generated comparable vaccinated and control groups. The Gambia study has been remarkably thorough in documenting a 90% success in prevention of the chronic carrier state, following a cohort for almost 20 years showing an unexpectedly (to many) long duration of protection of the vaccine, maintaining one of the most important cancer registries in Africa, and proving to many other African countries what can be achieved with HB immunization (4). However, it is still too early to measure a direct impact on PHC from this study.

Thus, the first reports directly measuring an impact on PHC in immunized cohorts of adolescents in Taiwan came as a surprise to most of the hepatitis community (5, 6). Adolescent PHC is rare, and only in a population with high rates of PHC and with careful disease surveillance could such a finding be established. The Taiwanese researchers must be commended: Taiwan continues to generate cutting edge research in the field of hepatitis.

In parallel and subsequent studies in Taiwan, researchers worked out the epidemiology of perinatal transmission of HB, showed that most perinatal transmission led to the chronic carrier state, and began a series of studies to explore how it could be prevented. First using HB immune globulin (HBIG), then HBIG plus HB vaccine, then HB vaccine alone, these studies, now confirmed by many others globally, have become an important basis for global public-health recommendations (7).

It is estimated that more than 2 billion people have serological evidence of current or prior HB infection, resulting in a pool of more than 350 million chronic HB carriers. Most of these carriers live in the high endemicity areas of Asia and Africa, where more than 8% of the populations are chronically infected. The use of HB vaccine in infants can reduce the carrier prevalence in immunized birth cohorts to less than 2% (low endemicity), and often to less than 1%. This has been demonstrated in Taiwan (8), Shanghai, rural China, Indonesia, Thailand, Gambia, Senegal, South Africa, American Samoa, in Alaska Natives, and in many other populations (9).

Although safe and effective HB vaccines have been available since 1982, immunization policies, economic constraints, and poor delivery infrastructure (in developing countries) have been impediments to the introduction of these vaccines. In the 1980s, the cost of a three-dose adult series of HB vaccine was more than $100,
making it impossible to consider for mass use in the developing world. At that time, strategies for using HB vaccine targeted primarily adult “high risk” groups, defined by lifestyle and occupation. Although the vaccines proved to be highly effective in protecting individuals, they had little impact on the incidence or prevalence of the disease, even in industrialized countries, because the only risk group successfully reached was health-care workers, who never represented more than 10% of cases in the community. Sexual and drug-related transmission, the major modes in the West, were never significantly reduced. In addition, immunization strategies targeting adults will never have a significant impact on liver cancer, which results predominantly from the asymptomatic infection of children and the subsequent carrier state. Therefore, in the 1990s, most industrialized countries began successful universal infant and/or adolescent immunization programs with HB vaccine (10).

In developing countries, it was clear that only universal infant immunization could modify disease rates, and the first hurdle was the price of the vaccine. Pioneering work by the International Task Force on Hepatitis B Immunization encouraged the production of HB vaccines in Korea and demonstrated the feasibility and impact of infant immunization programs in Thailand, Indonesia, and China (11). The price of HB vaccine fell to $1.00 per pediatric dose, and HB vaccine production technology was transferred to China, India, and Indonesia. During the 1990s, work by the World Health Organization stimulated vaccine introduction in 110 countries, including China and Indonesia. However, the poorest 72 countries, with more than one-third of the world’s birth cohort, could not afford the vaccine, and the global donor community that purchased most vaccines for them would not buy the relatively more expensive HB vaccine. In addition, only about 60% of children in these countries were being routinely immunized with the older cheaper vaccines for Bacillus Calmette-Guérin, polio, Diphtheria, Tetanus, Pertussis, and measles.

The low coverage rates and inability to introduce underutilized vaccines against HB, Haemophilus influenzae type B, and even yellow fever (available for more than 40 years!), led to the creation of GAVI and The Vaccine Fund approximately 3 years ago. GAVI is an alliance of the major partners in immunization: WHO, UNICEF, World Bank, the Bill and Melinda Gates Foundation, and representatives from developing-country governments, donor-country governments, the vaccine industry, foundations, nongovernmental organizations, and technical agencies. GAVI has a Board that is alternately chaired by the heads of WHO and UNICEF, as well as a small secretariat, task forces, regional working groups, and other structures. GAVI works through its partners on the ground in developing countries.3 The funding for GAVI activities comes from partner contributions and from The Vaccine Fund, started with an unprecedented gift of $750 million from the Bill and Melinda Gates Foundation, and now supplemented by donor governments to the level of approximately $1.2 billion.4

Developing countries with a per-capita gross national product of less than $1,000 may apply to GAVI and The Vaccine Fund for support for infrastructure strengthening, for HB vaccine and Haemophilus influenzae type b and Yellow fever vaccines (when appropriate) for 5 years, and for auto-disable syringes (which cannot be reused) for 3 years. In addition, GAVI and the Vaccine Fund support programmatic and R&D efforts designed to enhance the development and early introduction into the developing world of future vaccines against rotavirus, pneumococcus, and meningococcus A (the cause of epidemic meningitis in Africa).

In 3 years, 39 of the 72 poorest countries in the world have been approved to receive HB vaccine (vaccine is already flowing in 22 of these countries).5 In addition, the Chinese Government, GAVI, and The Vaccine Fund have developed an $80 million dollar project, that is 50% funded by the Chinese Government, which will allow Chinese infants to receive HB vaccine free of charge in the 12 poorest western provinces. Previously, although available, HB vaccine was sold to parents and only relatively wealthier families could afford it. In response to this program, the Chinese Government will make HB vaccine available to all Chinese newborns, free of charge. If this immunization is sustained, and there is every reason to believe that it will be, future birth cohorts of Chinese will have very low levels of HBV-related liver cancer that are similar to those of western countries.

In India, where HB vaccine is available on the private market but not through government programs, 30 major demonstration projects are being funded that will lead to routine use of HB vaccine for Indian children in the next 5-year plan, which begins in 2004. In Indonesia, GAVI funding will allow newborns, who already receive free HB vaccine, to receive the first dose of HB vaccine at birth at home. HB vaccine is being prefilled into a unique delivery device that cannot be reused; it allows birth attendants to store the vaccine un-refrigerated in their homes and to deliver it to children at home births. This early dose will increase efficacy against perinatal transmission, the mode most likely to lead to the chronic carrier state and a cancer outcome.

It was the research in Taiwan that taught us many of the lessons that are now being translated into global policy and implementation, and the work continues to help show the way.

References


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