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The impact of HPV vaccination delays in China: Lessons from HBV control programs

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It is well-known that vaccination efforts are often limited by available funds, despite being widely considered a cost-effective health intervention. In contrast, few consider the excess disease burden associated with vaccination delays due to failed health policy and bureaucracy. The history of the hepatitis B virus (HBV) vaccine in China is a case in point.

Worldwide, more than 240 million persons live with chronic HBV infection and increased risk for cirrhosis and hepatocellular carcinoma. In light of this enormous disease burden, some countries and areas implemented swift policy changes following the 1981 licensure of the first HBV vaccines. For example, Taiwan implemented a universal neonatal vaccination program in 1986 [1]. Soon after, in 1992, the World Health Organization (WHO) Secretariat recommended integration of HBV vaccine into national immunization programs by 1997. At the time of this recommendation, nearly one-third of all people with chronic HBV infection were Chinese.

With the development of a locally produced, safe, and efficacious vaccine by 1986, the Chinese vaccination effort evidenced a promising start. However, limited vaccine supplies restricted the 1988 campaign to neonates born to HBsAg positive mothers in selected areas [2]. Such setbacks continued, as exemplified by the Ministry of Health's 1992 universal neonate immunization initiative, which only achieved 70.7% HBV vaccine coverage by 1999. Furthermore, during this period uptake was grossly uneven with 99% coverage in Beijing but as low as 7.8% in some western regions [3].

This disparity has been ascribed to the financial burden of vaccination borne by parents [4]. Without government support or insurance company reimbursement, parents were responsible for all vaccination expenses. In 2002, the government began providing free vaccine while parents remained responsible to pay for vaccine administration [4]. However, substantial increases in vaccine coverage did not occur until 2005, when the government

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Author contributions

SMW performed the majority of the calculations, with contributions from DVC. DVC and SMW wrote the paper. Both authors read and approved the final version.

Conflicts of interest

Both authors report no potential conflicts.

began vaccinating neonates and children free of charge [4]. This resulted in coverage increasing to 95% in cities and 83.5–96.5% in rural areas [5].

A 2008 Chinese Ministry of Health report lauded the national vaccination policy as a great achievement, which successfully prevented 80 million new HBV infections and 19 million carriers between 1992 and 2006. However, these accolades did not account for costly implementation delays. We calculated that implementing the 2002 policies in 1986 could have prevented 64,000 hepatocellular carcinoma cases, 426,000 cirrhosis cases, 2,131,000 chronic hepatitis cases, and 8,524,000 cases of chronic HBV carriership (Table 1). Though often times spared the pathological sequelae of infection, Chinese HBV carriers endure lifelong social stigma and, until 2010, faced severe employment and educational discrimination.

The nearly 20-year delay in rollout of a nationwide HBV vaccination scheme comparable to Taiwan's provides an opportunity to identify roadblocks on the path to primary cancer prevention. First, since nationwide vaccine rollout is dependent upon Chinese national priorities, rather than WHO recommendations, the call to implement a vaccination scheme must arise from within the nation. Second, vaccine delivery in the context of China's enormous population, expansive geography, and strained healthcare system demand advanced planning and logistics. Finally, the Chinese population is sensitive to vaccination costs, and immunization plans must minimize the financial burden borne by the people. These are lessons to consider as we examine the status of the human papillomavirus (HPV) vaccination in China.

Based on the 1975 discovery of HPV's association with cervical cancer, the first HPV vaccine was licensed in 2006. In 2009, the WHO published its HPV vaccine position paper, which found the vaccine to be both safe and efficacious [6]. At present, most developed countries have integrated HPV vaccination into their national immunization programs. Furthermore, HPV vaccines have been licensed in numerous developing and newly industrialized countries, such as India, Thailand, Cambodia, Viet Nam, and the Philippines. Lamentably, China, which was estimated to have more than 75,000 incident cases of cervical cancer and 33,000 related deaths in 2008 [7], has not followed suit.

Despite WHO recommendations, HPV vaccination is expensive, with the cost of a three-dose regimen approaching US\$400 in some countries. This has prevented widespread use in the developing world, where more than 85% of cervical cancer and related deaths occur. Even with negotiated discounts, the cost of vaccination effectively precludes initiation of national campaigns in many countries where the vaccine is licensed. Nevertheless, for citizens of those countries with the means and desire, vaccine is available. In China, the vaccine is unavailable at any price.

Chinese State Food and Drug Administration regulations require all pharmaceutical companies seeking to license their products in China to perform a clinical trial in mainland China. Since the original global multicenter clinical trials for the WHO recommended HPV vaccines did not include mainland China, delays in vaccine availability were unavoidable. Efficacy endpoint data from Phase III Chinese trials of WHO recommended vaccines are not

expected until 2014 and Phase III primary endpoint data for Chinese domestic vaccine is not expected until at least 2016. Therefore, the availability of the HPV vaccine in China may be delayed by nearly 10 years.

This delay will result in substantial excess morbidity and mortality. Although the WHO recommended vaccination age is 9/10–13 years, HPV vaccination in China could be delayed until 15 years, due to the older age of sexual debut [8]. According to China's population and employment statistics yearbook, the country has approximately 59 million 9–15 years old girls. We calculated that a national HPV vaccination program of all 9–15 years old girls, between 2006 and 2012, could have prevented 1,971,000 HPV 16/18-related infections and 1,444,000 high-grade squamous intraepithelial lesion (HSIL) patients (Table 2). Moreover, we predict that there will be 381,000 cervical cancer cases and 212,000 related deaths in this population in the coming decades. Furthermore, each additional year of delay will cause 8,430,000 girls to lose their opportunity for vaccination. Of these girls, 282,000 are predicted to become infected with HPV16/18 and 206,000 are expected to develop HSIL and will be at high risk for cervical cancer over the next 25 years [9]. Therefore, in the coming decades, China will bear a considerable health burden that would have largely been preventable by existing vaccines.

Although screening programs can also reduce cervical cancer morbidity and mortality, the 2009–2011 attempts to screen 10 million rural Chinese women endured substantial challenges. Despite covering only 7% of women 35–59 years old, the project confronted shortages of gynecologists and cytologists in an already overburdened health care system. Due to incomplete coverage, inclusion of only two high-risk HPV types in current vaccines, vaccine failures, and the large number of women already infected, cervical cancer screening will continue to be needed for the foreseeable future. However, a nationwide vaccination scheme would reduce reliance on screening as the main method of cervical cancer prevention and may allow for effective implementation of a scaled down screening program that is less burdensome to the healthcare system.

At US\$9–13 per dose, HPV vaccination in China would be cost effective compared to screening only programs [10]. Though this is considerably lower than the cost per dose in developed countries, prices as low as US\$4.50 a dose were negotiated for the poorest countries in 2013. Though China will not qualify for this pricing, it may be able to negotiate the price down to cost effective levels. In addition, there is some evidence that two doses, or even one dose, of HPV vaccine may be as protective as three doses [11]. Regardless of the number of doses and the final cost for the series, more than a third of Chinese women are willing to pay only US\$3 or less for HPV vaccination [12]. Therefore, a successful immunization campaign will be dependent on the government subsidizing both the vaccine and administration.

Delayed universal, free HBV vaccination in China resulted in substantial excess HBV-related morbidity and mortality. Similarly, the costs of delayed HPV vaccination programs have already begun to accrue. To date, more than 140 countries and areas have approved the HPV vaccine. Given the vaccine safety and efficacy profile, we recommend that countries not included in the original global multicenter clinical trials license WHO approved HPV

vaccines based upon Phase II clinical trial data alone. If, as in China, Phase III efficacy data are mandated by SFDA, persistent HPV DNA infection should be considered as a surrogate endpoint, rather than precancerous disease, in order to expedite the approval process.

While awaiting the approval of HPV vaccine, we recommend that Chinese scholars establish an immunization schedule for nationwide vaccination of adolescent girls based upon WHO recommendations and the particulars of its sociocultural context. We also recommend that the government commence price negotiations with vaccine manufacturers and prepare logistics for equitable and efficient vaccine dissemination and delivery. Furthermore, we hope to work with media to raise awareness of the cost of vaccination delays among citizens and to garner the support of policy makers. In the interim, we hope that public health, reproductive health, health education, disease control, and immunization management professionals will actively seek opportunities for collaboration and cooperation, in order to increase vaccine acceptability and provide culturally appropriate education regarding the prophylactic nature of the vaccine.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Disease burden attributable to delayed HBV vaccination in China.

HBV Related Disease	Number of Cases		
	Total	Attributable to Non-Vaccination *	Attributable Fraction (%)
HBV carriers	11,501,822	8,524,100	74.11
Chronic hepatitis	2,875,456	2,131,000	74.11
Cirrhosis	575,091	426,200	74.11
Hepatocellular carcinoma	86,264	64,000	74.19

* The number of cases preventable by implementing the 2005 vaccination policies in 1986.

Table 2

Disease burden attributable to delayed HPV vaccination in China.

HPV Related Disease	Number of Cases		
	Total	Attributable to Non-Vaccination *	Attributable Fraction (%)
HPV 16/18 infected women	2,318,700	1,970,895	85.00
High grade squamous intraepithelial lesions	2,360,000	1,444,320	61.20
New cases of cervical cancer	531,000	381,390	71.83
Deaths of cervical cancer	295,000	211,884	71.83

* The number of cases preventable by vaccinating girls 9-15 years old between 2006 and 2012.