August 15, 2016

An Open Letter to:

President Xi Jinping and Premier Li Keqiang
The People's Republic of China

Subject: Ask for delaying implementation of HPV vaccination of Chinese children and young women

Dear President Xi and Premier Li:

I am a Chinese American and received my formal medical education and training in China from 1951 to 1961. I have practiced laboratory medicine in North America for more than 50 years and have serious science-based concerns about introduction of the human papillomavirus (HPV) vaccine, Cervarix™, as a means to prevent cervical cancer in China, as announced by GlaxoSmithKline (GSK), the HPV vaccine manufacturer, on 18 July 2016.

(http://www.gsk-china.com/en-gb/media/press-releases/2016/gsk-announces-cervarix-approved-in-china-to-help-protect-women-from-cervical-cancer/).

I am writing this letter to ask you to use your power to delay implementation of HPV vaccination in China until the risks versus benefits of mass HPV vaccination of Chinese children and young women age 9 – 25, as proposed by GSK, are adequately evaluated by independent medical/scientific experts who are not financially connected with the HPV vaccine manufacturers as is the case in the Western World. In the Western World, corporate allies have managed to use their public office to suppress factual information on the high frequency of serious adverse reactions among people after receiving HPV vaccinations in order to promote vaccine sales. One of such examples was documented in my open letter to the Director-General of the World Health Organization (WHO) posted in this link

http://sanevax.org/wp-content/uploads/2016/01/Allegations-of-Scientific-Misconduct-by-GACVS.pdf

My concerns are based on the following serious issues about HPV vaccines in general:

1. The fact is that HPV vaccination has not been shown to prevent a single case of cervical cancer in any country

To date, all clinical trial data used to support the claim of the efficacy of HPV vaccination to prevent cervical cancer have been based on using an epithelial change surrogate or a virology surrogate instead of "cancer" as the endpoints for statistical analysis. These surrogate

endpoints include the so-called cervical intraepithelial neoplasia 2 (CIN2) lesion that is really an equivocal ill-defined admixture of HPV infection and self-regressing precancerous changes in the cervical epithelium [1], or virology evidence of an HPV-16 or HPV-18 persistent infection as reported in a Chinese clinical trial sponsored by the vaccine manufacturer, GSK [2]. Since the CIN2 surrogate is an equivocal histologic diagnosis, not a true biologic entity, and the virology surrogate was based on HPV genotyping by Innogenetics SPF10 LIPA which is known to generate 9/12 "not proficient" test results as found by a WHO survey study [3], the claim of HPV vaccination being an effective means to prevent cervical cancer is open to question.

Indeed, GSK knows there is no evidence that the vaccine Cervarix™ protects women from cervical cancer, a fact supported by its announcement that states *"..favourable benefit risk ratio in preventing certain oncogenic HPV-related cervical diseases*..", not cervical cancer. However, the title of the announcement leads readers to believe the vaccine is effective in protecting women from cervical cancer when that statement remains to be proven.

2. GSK created a cervical cancer public scare to market a questionable HPV vaccine

In the U.S.A. there are 79 million women living with asymptomatic, largely harmless transient HPV infection without significant health consequences and about 14 million women become newly infected by HPV each year. Most healthy women infected with HPV can clear the virus in a few months. To put this into perspective, only 11,818 American women were diagnosed with cervical cancer with 3939 cervical cancer deaths in 2010. The majority of practicing gynecologists believe that most of these cancer cases could have been eliminated by further improvements in the healthcare delivery system for women. Cervical cancer is primarily a disease among unscreened or rarely screened women. Neither HPV infection nor cervical cancer is a national public health crisis in the U.S.A. or indeed anywhere else in the developed world. The reality is that manufacturers and their representatives working alongside and sometimes hand in hand with the government agencies along with their 'paid' academic consultants have created a cervical cancer scare to market and promote the sales of questionable HPV vaccines.

I found a similar misrepresentation in the GSK 18 July 2016 announcement which states "*Cervical cancer is the second most common cancer in women aged between 15 to 44 years in China, with an estimated 130,000 new cases each year.*" Based on a Report of Cancer Incidence and Mortality in China 2012 by Chen et al [4], the 10 top female cancer deaths (in X10000) in China in 2012 were due to lung cancer (18.3), stomach cancer (9.3), liver cancer (8.3), colorectal cancer (6.8), esophageal cancer (6.2), breast cancer (6.2), pancreatic cancer (3.3), cervical cancer (2.5) brain cancer (2.4), and leukemias (2.2). Since cervical cancer induced by HPV infection takes 15-30 years to develop, it is hard to believe that any reliable data has been collected on 15-year old females for analysis of the relationship between HPV infection and

cervical carcinogenesis. All Chinese health care workers know that cancers of the lung, gastrointestinal tract and liver kill far more women than cervical cancer. Given this however the Chinese health agencies should expand the preventive program against cervical cancer as it is the only cancer death that can be prevented if the malignant lesion is discovered early enough.

3. The HPV vaccines originally developed in South America may not work in China

HPV vaccines are genotype-specific. Gardasil® and Cervarix^{tm} were designed to target the L1 capsid proteins of HPV 16 and HPV 18 because it was assumed that these two high-risk genotypes are the causative agents of persistent infection which is associated with 70% of the cervical cancers world-wide. However, HPV 52 and 58 have been found to be as prevalent as HPV 16 and HPV 18 in the cervical cancers of a group of women patients living in Shanghai [5], suggesting that Cervarix^{tm} will not be effective against more than 50% of the cancer-associated HPV infections among the residents of Shanghai.

In addition, HPV 16 and HPV 18 strains found in patients of different parts of the world are known to have different variants. Each variant may have its own unique L1 capsid protein which in turn may be different from the antigen proteins contained in the vaccine, Gardasil® and Cervarix^{tm} developed primarily against the strains of HPV 16 and HPV 18 found in the residents of South America and North America. For example, there are three major subtypes of HPV18, namely the European, the Asian-American and the African subtypes [6]. All of the HPV18 isolates from European women were found to be those of the European or Asian-American variants [7]. In the United States, 91% of the HPV18 isolates from white women were reported to be of the European/Asian-American variants, and 64% of the HPV18 isolates from African American women belong to the African variants [8]. The vaccine manufacturers chose an African strain of HPV 18 (US patent 5820870) for HPV vaccine manufacturing. However, most of the HPV 18 strains found in patients in Thailand are related to the Asian-American and European types, raising questions about the effectiveness of the current HPV vaccines when used in Southeast Asia even against HPV 18 infections [6]. It is not clear if the HPV 18 strains infecting the Chinese women belong to the European/Asian-American variants or the African variants, or to another novel HPV 18 variant, as reported recently in a New York State proficiency survey sample [9].

Therefore, if the HPV vaccination proposal proceeds, the health agencies before implementing a genotype-specific HPV vaccine into the general population in China must obtain reliable HPV genotypes and subtypes infecting the Chinese patients in different regions. The HPV Vaccine Trials completed by the vaccine manufacturer and the NCI epidemiologists were initially conducted in a valley of Costa Rica where there is a high incidence of cervical cancer among its residents. The HPV genotypes selected for vaccine development for a small population in Costa Rica may not be suitable for all population groups in China.

4. Cervical screening as part of regular women's health care, not vaccination, is the priority

Cervical cancer is the most preventable cancer. In the United States, the widespread use of Papanicolaou (Pap) smear screening for detection followed by treatment of precancerous lesions reduced the incidence of cervical cancer from 44 in 100,000 women in 1947 to 8.8 in 1970. However, little information is available on cervical cancer screening behavior among the women in China. Very few Chinese women recalled having received a cervical screening [10]. It has been recognized that to prevent cervical cancer, national cervical cancer screening guidelines and comprehensive implementation strategies are needed to make screening services available and accessible to all women in China [10]. Highly sensitive HPV screening and reliable genotyping technology [11] may be used to identify those women with persistent high-risk HPV infection for cytology screening when qualified professional staffs for Pap smear screening are not readily available for the general women population in China. Since there are no treatments to cure the persistent HPV infections, prevention of cervical cancer is accomplished by physical removal of the cancer-susceptible transformation zone of the uterine cervical epithelium when a high grade precancerous lesion is detected by colposcopic biopsies.

5. HPV vaccination offers no added values

The GSK announcement stated *"Together with the cervical cancer screening programme, HPV vaccination will provide a better solution for Chinese women to fight against cervical cancer."* This statement admits that HPV vaccination should be used in populations with existent cervical cancer screening programmes already in place, and not be depended upon as a stand-alone measure for cervical cancer prevention. But at what cost? If we use the average cost of US$150 per dose of Gardasil® or Cervarix™ in the U.S. for calculation, each young female receiving 3 doses would cost the society $450 for this vaccine with no clear benefits in reducing the number of cervical cancers at all. The money if available for HPV vaccination should be used to educate more health care professionals for new screening programmes to improve women's health care in general. Furthermore, this GSK statement is highly misleading because to the uninformed readers it may suggest that HPV vaccination will provide a better solution than the screening programme for Chinese women to fight against cervical cancer which is far from the truth.

6. Serious adverse reactions after HPV vaccination programmes world-wide

Now it is widely known that HPV vaccination is associated with a much higher incidence of adverse reactions than other vaccine programmes used to prevent contagious diseases, for example the annual flu vaccines. The risk of unnecessary human sufferings associated with HPV vaccination probably outweighs the potential benefits of yet-to-be-proven reduction in cervical cancer deaths, a reduction which may occur 30 years after vaccine receipt, and deaths which

can be certainly prevented by improving any currently inadequate cervical screening programmes. Since the targeted HPV vaccinees are usually healthy teenagers, any serious adverse reactions following vaccination may have undesirable impacts on the normal physical development and normal education of these adolescents with serious negative life-long consequences.

The first HPV vaccine, Gardasil®, was licensed in 2006 in the U.S. and the second HPV vaccine, Cervarix^{tm}, was licensed in 2009. Shortly after introduction of Gardasil® into the U.S. market, many adverse reactions after HPV vaccinations were reported to The Vaccine Adverse Event Reporting System (VAERS), a national vaccine safety surveillance program run by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA). There were 12,424 reports of adverse events following Gardasil® vaccination received from June 1, 2006 through December 31, 2008, including 32 deaths with a mean age of 18 years old, who died 2 to 405 days after the last Gardasil® injection. Medical records and autopsy reports on 20 of the 32 deaths were available for review and confirmed there were 4 unexplained deaths and 6 cardiac-related deaths [12].

Syncope, Postural Orthostatic Tachycardia Syndrome (POTS) and sudden unexpected deaths at rest, in sleep, in the bathtub and under the shower among healthy active adolescent females are almost unheard of after receiving other vaccines, for example, the anti-flu virus vaccines. Many formerly healthy teenage females who received HPV vaccination developed permanent disabling disorders thereafter. These stories have been widely circulated on the internet, but rarely published in the medical literature due to a global editorial censorship of these case reports by mainstream medical journals.

HPV vaccination was approved in Japan in 2009. The Japanese Health, Labor and Welfare Ministry started recommending in April 2013 that schoolgirls aged 12 to 16 be vaccinated. However, the ministry suspended its proactive recommendation after just six weeks in response to complaints of side effects. The Japanese government has continued the suspension of its active recommendation after a public hearing on the safety issues associated with HPV vaccination on 26 February, 2014. The senior investigative reporter of Kyodo News, Mr. Mutsuo Fukushima, who helped organize the debate against the representatives of the vaccine manufacturer was forced to resign by Kyodo News thereafter, apparently under pressure from the vaccine manufacturer.

Of particular concern in connection with current discussions is another document, entitled “Clinical Review of Biologics License Application Supplement STN# 125126/773 – mid-adult women indication for GARDASIL” by Jeffrey N. Roberts, M.D. Medical Officer, Clinical Review Branch 2, Division of Vaccines and Related Products Applications, FDA, with a date of completed review on August 8, 2010.

http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM251763.pdf

In this document, it stated "*However, the vast majority of cases on the primary endpoint were persistent infection (PCR positive for one HPV type on two consecutive visits at least 6 months apart) or low grade cervical disease. Efficacy in the prevention of high grade cervical disease was not established*". It also stated under the section Death, "*A total of 8 deaths occurred during the study - 7 in the Gardasil group and 1 in the placebo group*." Under this statement, it listed **6 of the 7 deaths in the Gardasil group being Asian women; and the single one death in the placebo group was also an Asian woman.** This document clearly shows that the efficacy of Gardasil in preventing cervical cancer has not been established, and that HPV vaccination may be more dangerous to Asian women. Since both Cervarix™ and Gardasil® contain similar kind of active ingredient and placebo, the clinical trial data of the toxicity of Cervarix™ on Chinese females of different age groups within the targeted females from 9-29 should be published for public information.

As of today, various lawsuits have been filed against the HPV vaccine manufacturers in Japan, Costa Rica, Canada, Brazil, Ireland, France, Spain, Colombia and India. Only in the U.S.A., can the HPV vaccine manufacturers enjoy the benefits of marketing their vaccines without the fear of litigation since the Congresses passed a law in 1986 that gave companies protection from liability and set up the compensation program for vaccine injury. A US FDA statement in connection with the standards of polio vaccines in 1984 stipulates that "..*any possible doubts, whether or not well founded, about the safety of the vaccine cannot be allowed to exist in view of the need to assure that the vaccine will continue to be used to the maximum extent consistent with the nation's public health objectives.*"[13]. Apparently, the HPV vaccine patentees at the National Cancer Institute and Dr. Julie Gerberding, the then CDC director, were able to convince the FDA that the CIN2 changes and HPV 16 and HPV 18 infections which may lead to cervical cancer development should be regulated as a public health threat to the United States of America in 2006. For her involvement, Dr. Gerberding was rewarded with a lucrative job as vice-president of Merck's Vaccine Division after she left CDC in 2009, overseeing the sales of the HPV vaccine Gardasil®.

In May 2015, Dr. Gerberding sold 38,368 of her shares in Merck stock for $2,340,064.32 and still held 31,985 shares of the company's stock thereafter, valued at about $2 million, as reported https://web.archive.org/web/20150528003538/http://www.dakotafinancialnews.com/merck-co-evp-julie-l-gerberding-sells-38368-shares-mrk/159207/

7. Using aluminum adjuvant as placebo control to mask risk of HPV vaccination

In the CERVARIX™ HIGHLIGHTS OF PRESCRIBING INFORMATION, it states "Among females 9 through 25 years of age enrolled in these clinical studies, 6.3% of subjects who received

CERVARIX and 7.2% of subjects who received the control reported at least one serious adverse event during the entire follow-up period (up to 7.4 years)."

In the GARDASIL®9 HIGHLIGHTS OF PRESCRIBING INFORMATION, it states "Serious adverse events were collected throughout the entire study period (range one month to 48 months post-last dose) for the seven clinical studies for GARDASIL 9. Out of the 15,705 individuals who were administered GARDASIL 9 and had safety follow-up, 354 reported a serious adverse event; representing 2.3% of the population. As a comparison, of the 7,378 individuals who were administered GARDASIL and had safety follow-up, 185 reported a serious adverse event; representing 2.5% of the population. Four GARDASIL 9 recipients each reported at least one serious adverse event that was determined to be vaccine-related. The vaccine-related serious adverse reactions were pyrexia, allergy to vaccine, asthmatic crisis, and headache."

The manufacturers of both HPV vaccines used their proprietary aluminum adjuvant as the placebo in their clinical trial control group to mask the true adverse reactions caused the vaccines. This practice is considered inappropriate because the aluminum adjuvant is not an "inactive", or "inert" component in the vaccine formulation, and should not be used as the placebo in the control group for the following reasons:

Natural HPV infection of the uterine cervix evades local immune responses and does not cause viremia or systemic infection. Anti-HPV antibody levels as a result of natural HPV infection are usually not detectable. HPV vaccines containing virus-like particles (VLPs) comprised of recombinant L1 capsid proteins of specific HPV genotypes as the active ingredient are injected intramuscularly to stimulate genotype-specific antibody production by the host. A proprietary adjuvant called "Adjuvant System 04 (AS04)" which combines the TLR4 agonist MPL (3-O-desacyl-4'-monophosphoryl lipid A) and an aluminum salt is used in Cervarix^{tm} vaccine formulation to boost the host's immune response to the antigen to enhance antibody production. Another proprietary aluminum adjuvant, amorphous aluminum hydroxyphosphate sulfate (AAHS), is used for the HPV vaccine Gardasil® (Merck) to serve similar functions.

Aluminum salts in various forms have been used as adjuvants in vaccination empirically to boost immune responses of the host. However, the mechanism of the adjuvant effects of aluminum salts has only been recently investigated at the molecular level. It is now generally agreed in the scientific community that the aluminum salts used as adjuvants are cytotoxic and always damage the cells of the host at the site of injection, causing a localized inflammation at the vaccination site. This initial cell damage by the aluminum salt is an essential and necessary step to initiate its adjuvant effects because the free host DNA molecules released from the aluminum salt-damaged host cells act as mediators to trigger augmented immune responses of the host. The free DNA molecules of the dying host cells, also referred to as damage-associated molecular patterns (DAMPs) bind the aluminum salt adjuvant at the site of injection, and the

resulting DNA/aluminum complexes are phagocytized by the antigen-presenting cells (APCs) and macrophages. It was known as early as 2003, that when bound to aluminum salts as nanoparticles, free DNA molecules undergo dramatic conformational changes and can be introduced into mammalian cells as a means of gene transfection. In vaccination with aluminum adjuvants, the transfected host DNA activates the pathways that would increase their ability to interact productively with antigen-specific CD4 T cells to boost host immune responses.

In plain language, free DNA is needed to be carried by aluminum adjuvants into the APCs or macrophages to function as mediators for boosting immune responses in vaccination. Furthermore, since the active ingredients of the HPV vaccines are manufactured by inserting genetically modified HPV L1 gene DNA into yeast cells or insect cells for mass production, residual viral DNA in the form of recombinant HPV L1 gene DNA fragments are known to be present in the final vaccine products, according to an FDA announcement http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm276859.htm

Therefore, in addition to the host cell DNA generated at the site of injection, HPV vaccines are expected to contain viral DNA fragments as well. Being of a viral origin, HPV L1 gene DNA fragments are “non-self” microbial products, also referred to as pathogen-associated molecular patterns (PAMPs). The human body’s defense system can distinguish the PAMPs from the DAMPs in order to mount an appropriate immune response to either the presence of a pathogen or a tissue damage.

Equipped with a specially designed highly effective aluminum adjuvant and residual viral DNA fragments, HPV vaccination can cause the host to generate high levels of anti-HPV antibodies that natural HPV infections cannot, by inducing unusually strong innate immune responses with releases of a variety of cytokines from the macrophages at unpredictable timings and at unpredictable sites in the host’s body. However, these pro-inflammatory cytokines, including tumor necrosis factor (TNF)-α and IL-1β, may also contribute to adverse reactions, such as autoimmune diseases, acute disseminated encephalomyelitis, and myocardial damage, even sudden unexpected deaths in genetically and physically predisposed individuals. Aluminum adjuvants vary in their physical properties and their biological reactivity, and potential toxicities both at the injection site and beyond. Aluminum adjuvant engulfed by macrophages at the site of injection can be transported throughout the body including access to the brain [14].

Mass HPV vaccination of children and young women in the Chinese population will have complex impacts on society. I hope this letter can initiate open discussions with participation of stakeholders from various segments of the society before implementation of such a costly vaccine programme with uncertain benefits and substantial risk to the vaccinees.

I recommend that a Vaccine Adverse Event Reporting System (VAERS), similar to the one operating in the U.S. be established before implementation of an HPV vaccination programme in China if such a programme is allowed to go forward.

Thank you for your attention to this matter.

Respectfully yours,

Sin Hang Lee, MD, F.R.C.P.(C), FCAP

Director
Milford Molecular Diagnostics Laboratory
2044 Bridgeport Avenue
Milford, CT 06460
USA
Email: shlee01@snet.net
Telephone: 203 878-1438
Fax 203 878-0109

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