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Refutation of Global Advisory Committee on Vaccine Safety "Statement on Safety of HPV Vaccines: 17 December 2015"

I. Overview of the GACVS Statement and the situation in Japan

Human papilloma virus (HPV) vaccines were approved relatively late in Japan compared with Western countries (October 2009 for Cervarix and July 2011 for Gardasil). The vaccination rate was low at the beginning; however, after an HPV-vaccine promotion campaign that led to government subsidization of the cost of the vaccine in November 2010, the vaccination rate increased exponentially, followed by an unexpected increase in adverse event (AE) reports. Within 3 months of the formal designation as a routine vaccination, the Ministry of Health, Labour and Welfare (MHLW) withdrew its active recommendation on the grounds of "an undeniable causal relationship between persistent pain and the vaccination"[1].

However, in a statement released on December 17, 2015, the World Health Organization (WHO) Global Advisory Committee on Vaccine Safety (GACVS) claimed that it had "not found any safety issue that would alter its recommendations for the use of the vaccine" and that, "the impact of HPV vaccines on HPV-related clinical outcomes, including precancerous lesions is well established". Direct criticism was leveled at Japan in the form that, "policy decisions based on weak evidence, leading to lack of use of safe and effective vaccines, can result in real harm"[2].

This unwarranted criticism shows not only incorrect understanding of the situation in Japan regarding AEs following HPV vaccination but mistaken assessment of the vaccine's risk-benefit balance. It also disregards the fundamentals of health policy-making, namely that appropriate preventive measures should be established by each individual country taking into account the state of disease prevalence, hygienic environment, education, and economic status in that country. The main problems arising from the GACVS's stance are outlined below.

II. Safety

(1) AE reporting in Japan

Table 1 shows the number of serious adverse event (AE)/adverse drug reaction (ADR) reports, as defined according to the ICH E2A guidelines,[3] submitted for HPV vaccines by the vaccine makers and medical professionals as of the end of February 2016[4].

These numbers far exceed those for other vaccines[5-14] (Figs. 1 and 2). As these data are compiled from voluntary reports, the actual incidence of AEs may well be far higher[15,16]. Countries other than Japan have also indicated major problems with the safety of HPV vaccines[5,17]. Ignoring these "inconvenient" facts in an effort to promote HPV vaccination contradicts the primary responsibility of WHO, which is to dispassionately assess risks and benefits.

Table 1: Serious AE/ADR reports of HPV vaccines in Japan[4]

	Total Doses*	Total Number of Inoculated Persons*	Serious AE/ADR reports	
			From MAH	From Med. Institut.
Cervarix	**6,998,266**	**2,590,000**	**835**	**448**
Gardasil	**1,924,121**	**800,000**	**124**	**165**

*Estimated from sales data

AE: adverse event; ADR: adverse drug reaction; MAH: marketing authorization holder

Observation period: Cervarix: 2009 Dec～2016 Feb Gardasil: 2011 Aug～2016 Feb

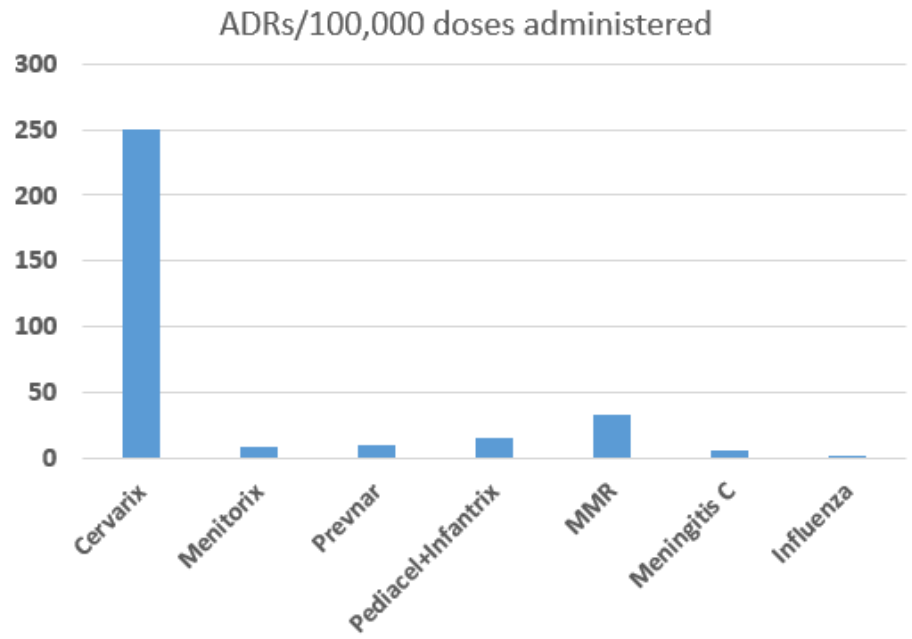

Fig. 1: The rate of ADRs from Cervarix compared to other vaccines in the United Kingdom immunization schedule[5,9)]

Data sourced from the report provided by the United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA) for the Joint Committee on Vaccination and Immunisation, June 2010. MMR: measles, mumps, and rubella.

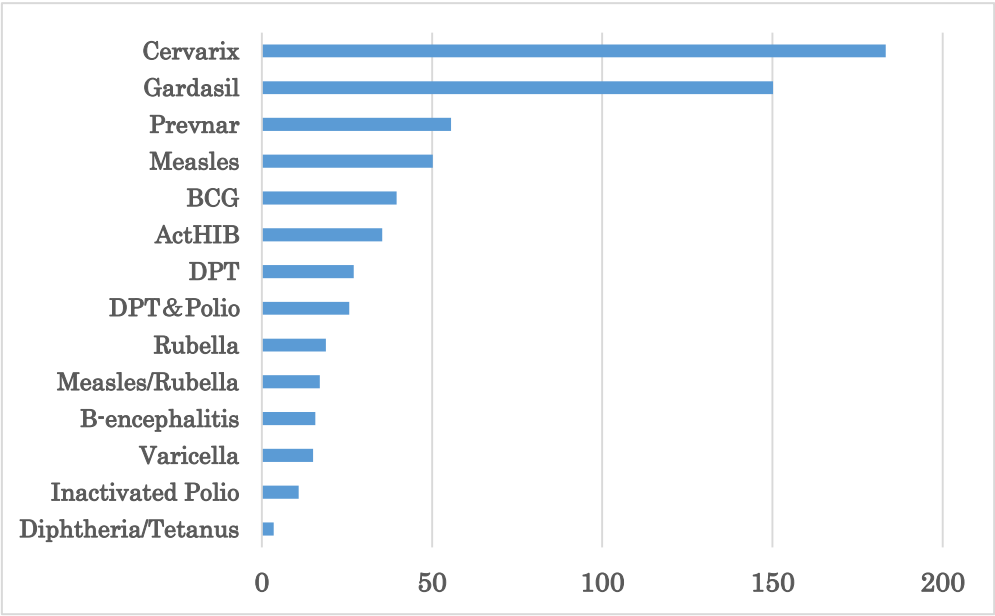

Fig. 2: Severe ADRs from HPV vaccines and other vaccines in Japan[6-8)] (ADRs/10^6 inocul.)

BCG: Bacille Calmette Guerin; DPT: diphtheria-pertussis-tetanus

Reported serious AEs include diverse, complex, multi-system symptoms such as seizures; disturbance of consciousness; systemic pain including headache, myalgia, arthralgia, back pain and other pain; motor dysfunction such as paralysis, muscular weakness, exhaustion, and involuntary movements; numbness and sensory disturbance; autonomic symptoms including dizziness, hypotension, tachycardia, nausea, vomiting, and diarrhea; respiratory dysfunction including dyspnea and asthma; endocrine disorders such as menstrual disorder and hypermenorrhea; hypersensitivity to light and sound; psychological symptoms including anxiety, frustration, hallucinations, and overeating; higher brain dysfunction and cognitive impairments including memory impairment, disorientation, and loss of concentration; and sleep disorders, hypersomnia and sudden sleep attacks. In some cases, these symptoms impair learning and result in extreme fatigue and decreased motivation, negatively impacting everyday life[11-14]. In the following sections, these diverse symptoms will be referred to as "post-HPV vaccination symptoms".

Many of these symptoms also overlap with complex regional pain syndrome (CRPS), postural orthostatic tachycardia syndrome (POTS), chronic fatigue syndrome (CFS), and fibromyalgia syndrome (FMS). Thus, patients who present symptoms after HPV vaccination are labeled with various diagnoses and the medical community has made little effort to comprehensively view the symptoms as an overall disease state caused by vaccination. Patients are placed into the category that best approximates their symptoms from existing disease concepts and are interpreted simply as "misfits" in whom symptoms coincidentally happened to appear after vaccination. Patients who ultimately cannot be given a formal "diagnosis" are treated as if they are having psychogenic reactions or have a malingering disorder, and such treatment causes patients further emotional distress. This problem is not limited to Japan, and other countries have reported many patients in similar situations[5,17].

Under these circumstances, the WHO and national health authorities should not immediately rule out a causal relationship with the vaccine. Rather, when faced with such a situation, it is their responsibility to collect case reports, including disputable cases; conduct detailed interviews about AEs; and undertake the necessary case-control and cohort studies based on the emerging clinical data.

(2) Investigation by the MHLW

Regarding Japan, the GACVS statement says that, "review of clinical data by the national expert committee led to a conclusion that symptoms were not related to the vaccine"; however, there are major problems with the expert committee's investigation.

On January 20, 2014, the expert advisory committee established by the MHLW presented the view that the diverse pain and motor dysfunctions experienced by many individuals after HPV vaccination comprised psychosomatic reactions to anxiety or stimulatory pain caused by needle injection and were not due to vaccine components. [18)]

However, the members of that committee included very few doctors who have actually examined patients with post-HPV vaccination symptoms. Furthermore, the committee's investigation focused exclusively on pain and motor dysfunction and ignored the many other diverse post-HPV vaccination symptoms that have been observed. Usually, in a drug regulatory agency, assessors classify and code ADR reports according to a dictionary such as MedDRA (Medical Dictionary for Regulatory Activities) or ICD10 (The 10th revision of the International Statistical Classification of Diseases and Related Health Problems), and look for evidence that the medicine was the cause, which makes it difficult to act based on the actual reports. Detailed descriptions can tell us much that we do not know and yet need to know, but these descriptions mostly do not appear in the coded reports. The conference minutes of the expert advisory committee on the HPV vaccine show that the committee held only a cursory discussion in which causality was denied[18)]. Cases in which symptoms appeared more than 1 month after vaccination were excluded from investigation; however, subsequent study has clarified that symptoms commonly manifest even after a considerable period of time has elapsed since vaccination[11,13)]. In addition, data published by the French National Agency for Medicines and Health Products Safety[19)], which was quoted in the GACVS statement, also included a much longer surveillance period; specifically, the median time between final vaccination and onset of Guillain-Barre syndrome was reported to be 4.6 months with an interquartile range of 0.9-11.3 months. Consequently, the MHLW itself subsequently extended the observation period.

The methods used for determining psychosomatic reactions to be the cause of symptoms are also open to question[18)]. The expert advisory committee proposed the following possible causes for post-HPV vaccination symptoms: 1) neurological disorder, 2) intoxication, 3) immunological reaction, and 4) psychosomatic reaction. For causes 1), 2) and 3), if there were any contradictory findings at all, the possibility was dismissed. For cause 4), if there were any suggestive symptoms, the cases were accepted as psychosomatic while contradictory findings were ignored. This approach is arbitrary and thus the conclusion is not warranted based on the methodology.

Support for the expert advisory committee's conclusion remains far from universal. Doctors and researchers who have actually examined patients with post-HPV vaccination symptoms have criticized the conclusion and pointed out that it is difficult

to explain all symptoms as psychosomatic reactions. Furthermore, as 11 of 15 members of the expert advisory committee have direct relationships with vaccine manufacturers, the public is justified in requesting that a more diverse range of scientists review the relevant data[20]. Thus, the safety of the HPV vaccine remains far from certain in Japan, justifying the public's strong concerns.

(3) Criticism of the evidence for safety mentioned in the GACVS statement

Regarding the safety of the HPV vaccine, the GACVS statement claimed it had not found any safety issues that would alter its recommendations for the use of the vaccine and criticized Japan's decision to stop actively promoting HPV vaccination. However, the studies[19,21-25] cited by the GACVS as evidence for the vaccine's safety raise the following fundamental questions:

i) Genetic basis of autoimmunity

Most autoimmune diseases are complex polygenic conditions in which affected individuals inherit multiple genetic polymorphisms that contribute to disease susceptibility, and these genes interact with environmental factors to cause the disease. It is a well-known fact that some Human Leukocyte Antigen (HLA) alleles occur at a higher frequency in patients with certain autoimmune diseases than in the general population[26].

The alleged primary evidence at present for the safety of the HPV vaccine is that there is no statistically significant difference in the incidence of autoimmune diseases in vaccinated females compared to unvaccinated females or the general population. However, since the proportion of genetically susceptible people in the general population is very small and limited, simple comparisons of the incidence of autoimmune diseases between those who have been vaccinated and a control (unvaccinated) group are likely to show no significant difference. Therefore, arguments that do not take this issue into consideration cannot assure the safety of this vaccine. Many autoimmune diseases have a relatively low baseline prevalence; therefore, careful, large-scale post-marketing surveillance that bears in mind the immunological characteristics of individual patients is required to scientifically verify the relationship between vaccination and autoimmune diseases[27].

ii) Coding and concealment of "inconvenient" facts

In drug regulatory agencies and the pharmaceutical industry, all AEs in a patient's medical record are coded for computer processing and thus details contained in the raw

data are “lost” which has the effect of masking the clinical significance and extent of drug risk[28,29]. This approach amounts to nothing more than simply isolating and retrospectively analyzing each post-HPV vaccination symptom within the framework of existing disease concepts rather than viewing the symptoms comprehensively.

iii) Paradigm shift

HPV is equipped with various immune evasion mechanisms, which could cause the immune system to become more tolerant to the infection, creating a microenvironment susceptible to further infection and facilitating progression of cervical intraepithelial neoplasia (CIN). To counteract these immune evasion mechanisms, the HPV vaccine is designed to maintain an extraordinarily-high antibody level for more than a decade[30,31], and this shifts the HPV vaccine out of the paradigm of a “vaccine” as we conventionally understand it. In light of these unique characteristics of the HPV vaccine, a more thorough evaluation of its safety is essential.

III. Effectiveness

While the GACVS statement claims that, “the impact of HPV vaccines on HPV-related clinical outcomes, including precancerous lesions is well established”, in actuality, the effectiveness of the HPV vaccine is quite limited, as discussed below.

(1) Limitations of effectiveness

First, the only verified effect of the HPV vaccine is a preventive effect on precancerous lesions (specifically CIN); the preventive effect on cervical cancer itself has not been established. Furthermore, the effects of the vaccines that are currently approved in Japan (Cervarix and Gardasil) on precancerous lesions have only been demonstrated for HPV 16 and 18, which according to the most reliable studies represent only 50% of cervical cancer cases in Japan[32].

Furthermore, 10% or less of cases of high-risk HPV infection result in persistent infection that can cause cancer, while the large majority of any precancerous lesions (CIN) that do develop resolve before becoming cancer [33,34]. Therefore, only 0.15% of individuals infected with high-risk HPV develop (invasive) cancer[35,36]. Even if cancer occurs, with regular checkups it can be detected at an early stage and appropriate treatment (surgery, radiation, and chemotherapy) saves many lives. Based on these facts, promoting educational activities emphasizing the importance of screening and early detection, and providing an environment in which women feel more comfortable undergoing Pap testing, would be far more effective at preventing cervical cancer, rather

than pressuring teenage girls to receive the existing HPV vaccination, with all its problems.

Proponents of these vaccines often state that HPV vaccines are 98-100% effective in preventing cervical cancer; however, these figures represent the percentage of relative risk reduction (RRR). RRR can easily lead to misunderstandings and it is sometimes intentionally misused to exaggerate both benefit and harm[37,38]. In reality, the absolute risk reduction (ARR) expected by HPV vaccines is at most 0.1-0.7%. Furthermore, this only indicates the risk reduction of developing precancerous lesions, while the risk for cervical cancer remains unknown.

(2) Cancer screening as an alternative measure

Promoting cervical cancer screening is another important measure against cervical cancer. The low screening rate for cervical cancer in Japan compared to Western countries has long been pointed out. In particular, young women with no experience of pregnancy are reluctant to undergo gynecological examinations in Japan. Accessibility to examinations by female doctors and acceptance of self-sampling would undoubtedly increase the screening rates. Improving and promoting screening methods in this way would markedly decrease the cervical cancer mortality rate[39].

IV. Conclusion

The proponents of the HPV vaccine often state that only a fraction of individuals who undergo HPV vaccination will experience AEs and the risks need to be weighed against the benefit of cancer prevention. However, complaints of AEs and cases of serious and protracted symptoms are more numerous for the HPV vaccine than for other vaccines. The situation in Japan is similar to that in other countries, which also report a picture of a specific cluster of serious and complex symptoms that develop across multiple body systems over an extended period of time.

Girls who have previously enjoyed good health are suddenly tormented by pain and worry, and their life dreams and aspirations are put on hold. Symptoms following HPV vaccination can result in major disadvantages that seriously impair a wide range of aspects of daily life such as inability to do even simple calculations, severe memory impairment and learning disabilities, problems with walking, becoming bedridden due to pain and motor dysfunction, and giving up seeking a higher education. In addition to the huge social costs, lives and human dignity have been ruined.

Furthermore, treatment for these symptoms has yet to be established and no method currently exits for identifying individuals likely to be susceptible to serious AEs. The

mortality rate from cervical cancer in Japan is being maintained at a low level comparable to that in Western countries. Therefore, balancing the serious concerns regarding the safety of the HPV vaccine against its limited effects, there is no compelling reason for Japan to recommend vaccination. The Japanese government's decision to stop actively promoting HPV vaccination in light of the current situation is justified; the GACVS's criticism of this decision is not.

Despite not conducting its own investigation into the symptoms following HPV vaccination, the GACVS is nevertheless criticizing the independent policies of Japan, one of its member countries, while attempting to compel compliance with specific policies using only the force of authority as the basis. This criticism constitutes a failure of the WHO to live up to its responsibility as an international body having the stated goal of strengthening health systems, and it is a criticism to which we strongly object.

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