

# AMSA Japan: The HPV vaccine crisis in Japan

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## Introduction/ Background

Cervical cancer is the fourth most common cancer in women, and a major public health problem both in developing and developed countries, with an estimated 570 000 new cases and 311 000 deaths in 2018 according to data from GLOBOCAN.<sup>1</sup>

Most cervical cancers are caused by Human papillomavirus (HPV), which can be prevented by HPV vaccine. Therefore, HPV vaccine provides effective primary prevention against cervical cancer. The first-generation quadrivalent and bivalent HPV vaccines, which provide protection against HPV types 16 and 18 that are together responsible for about 70% of cervical cancer cases globally.<sup>2</sup> A second-generation nonavalent HPV vaccine, which provides protection against 9 HPV types, can prevent up to 90% of cervical cancer causes.<sup>3</sup> After 14 years since its introduction in 2006, HPV vaccine has been proven to be safe and effective against cancers caused by HPV infections.<sup>4,5,6,7,8</sup> Combined with cervical screening, rapid scale-up of HPV vaccination can make cervical cancer elimination achievable in most countries.<sup>9</sup> In August 2020, the World Health Assembly has called for a global strategy to accelerate cervical cancer elimination, emphasizing the importance of prevention through vaccination as one of the three main pillars.<sup>10</sup>

In Japan, the bivalent vaccine Cervarix® and the quadrivalent vaccine Gardasil® were licensed in 2009 and 2011, respectively. Both vaccines were temporarily publicly funded in December 2010, and were included in the national immunization program (NIP) in April, 2013 and were given for free for girls aged 12-16 years. However, soon after its introduction in the NIP, several reports of adverse events following vaccination began to appear in the media, raising questions about the vaccine safety profile. In June 2013, the Ministry of Health, Labor and Welfare (MHLW) decided to suspend the proactive recommendation for the HPV vaccine, and stopped all the vaccine promotion programs.<sup>11</sup> Repeated reports of adverse events and lacking the government's endorsement caused the HPV vaccination rate plummet from 73% to 0.6%, even though the vaccine is still being part of the NIP and free.<sup>12</sup> After 7 years, the Japanese government still has not changed their stance towards HPV vaccine recommendation, and the HPV vaccination rate has stagnated at below 1%.<sup>13, 14</sup> Combined with the low cervical cancer screening rate of only about 30%, Japan might have lost a real opportunity to decrease cervical cancer's morbidity and mortality. While other developed countries are on their way to eliminate cervical cancer, the incidence and mortality of cervical cancer have been increasing in Japan, with young women becoming the most vulnerable.<sup>15</sup>

Clusters of adverse events following immunization (AEFI), media reports and rumors about vaccine safety can erode public's trust, resulting in vaccine hesitancy. This was seen in many countries other than

Japan, such as Ireland and Denmark.<sup>16,17</sup> Due to its global significance, in 2019, WHO has listed vaccine hesitancy as one of top ten threats to global health.<sup>18</sup>

Lacking communication strategies and failure in crisis management can be detrimental to the vaccine programme, resulting in a widespread vaccine crisis, as seen in Japan. This white paper discusses major problems surrounding the HPV vaccination programme in Japan, and proposes some policies and solutions to improve the status quo.

## Outline problems

### **The MHLW's decision to suspend the vaccine recommendation and problems in the current vaccination policy**

The MHLW's decision to suspend the proactive recommendation for HPV vaccination in June, 2013 was made hastily due to the pressure from the public and media about the unconfirmed severe adverse events, without presenting any scientific evidence. The decision was taken by 3:2 vote among government bureaucrats of the Vaccine Adverse Reactions Review Committee (VARRC),<sup>11</sup> despite the favorable evidence of HPV vaccine cost-effectiveness in Japan<sup>19</sup> and WHO declaration of vaccine safety just one day before. Such an important decision that required careful consideration should have been made by an independent advisory committee, such as the Advisory Committee on Immunization Practices (ACIP) in the USA, rather than a committee held by government bureaucrats.

After that, there have been many national studies about the reported adverse symptoms in Japan. The Nagoya study<sup>20</sup> after conducting a survey of 29,846 female residents of Nagoya City born between April 2, 1994 and April 1, 2001, suggested that there was no causal association between the HPV vaccines and 24 reported symptoms. The MHLW, after clinical evaluation of individual cases, also stated that the reported symptoms were not causally associated with the HPV vaccination but were psychosomatic responses.<sup>21</sup> 17 academic associations including the Japan Society of Obstetrics and Gynecology (JSOG) and the Japan Pediatrics Society (JPS) also called for a restart of the HPV vaccination recommendation.<sup>22</sup> Nevertheless, despite all the national and global evidence of vaccine safety and effectiveness, the government has not shown any signs of changing their stance, and the temporary withdrawal of the vaccine recommendation lasted until now.

This is not the first time Japanese government has shown its weakness in managing the Adverse Events Following Immunization. The measles, mumps, and rubella (MMR) vaccine, after its introduction in 1989, was withdrawn in 1993 due to reports of unexpectedly high rates of aseptic meningitis associated with a vaccine's component.<sup>23</sup> The withdrawal was followed by changes in the country's immunization

law, such that all childhood immunizations were no longer mandatory. The Japanese government being very passive in the formulation of vaccine policies resulted in a low measles vaccine coverage, and a measles epidemic occurred in the following years.<sup>23</sup>

Failure in HPV vaccination program and prior's experience with the vaccine programme cause Japan lagging behind in controlling vaccine-preventable disease. Despite being a developed country with high healthcare standard, Japan is known internationally as a "vaccine backward country" (ワクチン後進国).

The reason behind this problem lies in the fact that there is a lack of experts with highly specialized knowledge in infectious disease or immunization in the MHLW. There is no independent organization for decision making on immunization, such as the Advisory Committee on Immunization Practice (ACIP) of the US.<sup>24</sup> Therefore, issues on immunization, which should be discussed based on scientific evidence, belong to the political side at present. Decisions about vaccination have been made based on political factors, rather than based on scientific evidence or for the purpose of promoting public health.<sup>24, 25</sup>

### **Biased media coverage**

Biased coverage of unverified negative information about HPV vaccine by the media is another problem. Media plays a key role in changing the public's health behavior.<sup>26</sup> Since the media, especially television or newspapers, remains the most credible source of information, and is accessed daily by most Japanese people,<sup>27</sup> the contents covered by the media can either positively or negatively affect the parents' and daughters' attitude towards the vaccine. The crisis began after a sensational report by Asahi Shimbun, one of the most authoritative and influential newspapers in Japan, of a junior high school student who allegedly suffered from walking abnormalities following immunization in March 2013. Since then, newspaper coverage of anti-vaccination contents, such as on adverse effects to vaccines, alleged victims, and related lawsuits significantly increased, whereas pro-vaccination contents, such as evidence of vaccine effectiveness and safety scarcely appeared.<sup>28</sup>

### **Flawed study on vaccine safety further increased hesitancy**

To make the situation worse, some medical professors have come forward to publicly support the claim that the HPV vaccine may cause the reported adverse events. A research group proposed a novel disease titled "HPV Vaccination Associated with Neuropathic Syndrome (HANS)" for the set of diverse physical and psychological symptoms appearing after HPV vaccination.<sup>29</sup> They even claimed that once the symptoms appear, they will not go away and there is no established treatment. In 2016, the group published their experimental result using the mice

model, proposed hypothalamic destruction with vascular cell apoptosis after admission of HPV vaccine as an explanation for HANS. However, their paper was retracted in 2018 due to an inappropriate experimental approach.<sup>30</sup>

Also in 2016, professor Shuichi Ikeda, one of the leaders of the HPV vaccine adverse reaction research teams designated by the MHLW, presented at the Joint Meeting VARRC that the vaccine caused nervous system damage based on the result of research on mice. The research, before proven fraudulent, was largely shared by the media, causing devastating impact to the public's attitude toward HPV vaccine.<sup>31</sup> All those events have resulted in a very negative public's attitude toward the HPV vaccine.

A survey showed that Japanese mothers overestimate the frequency of the severe adverse events 10-1000 times, while underestimate the burden of cervical cancer.<sup>32</sup> Meanwhile, the government's complete silence and lack of addressing the rumors from media and anti-vaccine groups, largely contributed to erosion of public trust in HPV vaccine.

### **The Japanese government shows some movement 5 years after the suspension**

In 2018, as an effort to improve the stagnated HPV vaccine coverage, the MHLW published HPV vaccine leaflets as an official document from the government, with the aim to provide the public with the correct and verified information of HPV vaccine.<sup>33</sup>

The dissemination of this leaflet was anticipated to improve the situation; however, at the 42th meeting of the VARRC, a survey conducted by MHLW showed that 70% of municipalities did not use the leaflet in any forms, such as posting the leaflet on their homepage website, displaying at the information desk or actively distributing it.<sup>34</sup> Public awareness of the leaflet was extremely low, 86.3% answered that they have never seen the leaflet before.<sup>34</sup>

The content of the leaflet was also criticized for not having a clear target audience, containing too much information, and using many medical jargon and complex medical terms that are difficult to the public. The expression "the recommendation of the vaccine is temporarily stopped", which is strongly emphasized at the end of the leaflet, can be misunderstood as a conclusion that "you should not take the vaccine"<sup>35</sup>. A survey asking Japanese mothers whose daughters were of the HPV vaccine-targeted age (were of the targeted age for receiving vaccine) showed that the mothers having negative attitudes toward the vaccine before reading the leaflets were still negative about the vaccination even after reading the leaflet.<sup>36</sup> Those results imply that there is a need for improvement in both the content of the leaflet and the method of disseminating it.

### There are some good signs recently

Recently, on October 9th the MHLW released a new version of the leaflet, after hearing from experts in the fields of risk communication and public relations.<sup>37</sup> The revised leaflet will be sent individually to the vaccine-targeted girl and their parents by the municipalities.<sup>38</sup> The nine-valent vaccine has finally been approved, 5 years after its submission.<sup>39</sup> Increase in the burden of cervical cancer as a consequence of the decline in HPV vaccination has also started to be broadcasted by the media.<sup>40</sup>

### The reason why Japanese government still not recommend the HPV vaccine.

The anti-vaccine group established by parents of girls who had developed the symptoms after immunization is the key stakeholder. When the MHLW released their investigations results that there were not causal relations between the vaccine and reported event in 2016, the group opposed strongly by accumulation of the voice of the HPV vaccine “victims”. Some of those contains very sensational messages such as “the results did not include me”, or “I do not care about the result, just give me the treatment”, “Give me back my body before vaccinated”.<sup>42</sup> The group strengthened their activities and established National Attorneys Association for the HPV Vaccines Lawsuits in Japan<sup>43</sup>, with the aim to raise a lawsuit against the government and the pharmaceutical company for a compensation due to HPV vaccine adverse events.

## Proposed policy

In Japan, mothers are the one who decide whether their daughter get the vaccine or not. According to the latest research about Japanese mother’s attitude, most of them know about the vaccine and cervical cancers, but only 10% willing to let their daughter be vaccinated under the current situation, implying great hesitancy of Japanese mothers towards the vaccine.

Proactive and robust communication campaign, from developing to spread the message by involving multi-sector collaboration should be implemented to counter the situation.

### Developing the message

Immunization is special in the way that the precautionary measure (vaccination) in itself implies risk. Even though it is evident to health authorities that the benefits of vaccines outweigh the risk, this may not be the obvious conclusion for all. Instead of making a rational decision based on accurate facts, people tend to rely on their emotions or cognitive shortcuts, which is known as heuristics in behavioral economics.

To bridge this "risk perception gap" between health authorities and the public, the message should be simple, easy-to-understand and convey more than just dry facts.<sup>44</sup>

On October 9th, 2020, the MHLW released a revised version of leaflet<sup>37</sup> as an official message that will be sent individually to the vaccine targeted girls and their parents. We analyzed whether these modifications are effective in motivating mothers to get their children vaccinated.

The revised leaflet makes use of the safety effect<sup>44</sup>, which is the tendency to value losses over gains by highlighting the seriousness of cervical cancer, the risk of not taking the HPV vaccine. It presents the morbidity and death rate of cervical cancer by translating the standard “out of 10,000 people” statistics into more relatable figures such as prevalence rate in terms of a class size of 40 students. Percentages were also conveyed using visual graphs instead of numeric values.

Nonetheless, there is no part writing about vaccine safety in the current leaflet. Japanese mothers have a lot of concerns about the vaccine safety. Stating that the vaccine is extremely safe by showing the robust evidence from both global and national studies can make mothers feel more confident about the vaccine. Moreover, the current way of writing about the vaccine risk “The severe adverse event is rare, it can happen in 5 out of 10000 people” can intensify the fear in vaccine. According to the prospect theory, people tend to overreact to events with small probability while underreacting to events with high probability in accordance to the probability weighting function<sup>45</sup>. Because the risk of vaccine happens immediately while the benefits are in the future, the probability of an adverse event in HPV vaccination is 0.007% can cause people to overreact to a point where most of the population do not want to take the vaccine. A new section should emphasize the “side-effect free rate” of the HPV vaccine to be 99.995% and provide case examples of what treatment can be done if adverse events were to happen. Emphasis on safety and a willingness to act quickly to amend adverse cases is imperative to regain the public trust. Including narrative in addition to statistics, from a female who experienced cervical cancer, or from a mother whose daughter suffering from cervical cancer may also be both effective in motivating the mothers to get their children vaccinated.<sup>46</sup>

Currently leaflet is the only official material from the government. Other types of messages, such as public poster, fact sheet, or decision aid should also be considered.

### **Disseminate the message**

Thorough and repeated dissemination of the message by using multiple mediums to ensure that the correct information get to the public. Multi sector collaboration among Japanese government, municipalities, social media, and school is necessary to achieve this goal.

### **Municipalities:**

The system of information provision had been criticized for leaving everything to the discretion of the local governments, creating the disparity among regions because different municipalities have their own

way of disseminating the information.<sup>47</sup> This is shown by the fact that 70% of the municipalities did not use the MHLW leaflet to provide information.<sup>34</sup>

Recently, the MHLW has strengthened the policy such that “Information provision should be implemented, regardless of local governments, as part of the public dissemination based on the Enforcement Ordinance of the Preventive Vaccination Law”<sup>48</sup> to ensure a thorough information provision among all prefectures. With this decision, the new version of the leaflet will be individually delivered to girls eligible for the vaccine and their parents. Nonetheless, the government needs to continuously monitor the implementation status of each local government, to ensure that the information provision is conducted thoroughly, and act promptly in case information is not delivered sufficiently.

Moreover, repeatedly presenting information of HPV vaccine by using posters in public places such as train stations, airports or large department stores should be helpful to catch the public’s attention. The municipalities should also take active communication with the relevant medical institutions to provide parents and their daughters with the correct information, answer their concerns, and ensure smooth inoculation.

### **School:**

The vaccine awareness in 12-16 years old girls is extremely low, with 40% said that they have never heard of the vaccine effectiveness, nor knowing about the adverse events that can happen. They also replied that school is the place that they want to get the information from.<sup>34</sup>

Thereby, organizing events to conduct lessons about cervical cancer and HPV vaccine at school should be effective in increasing the girls’ awareness. Having their mothers accompany, and letting them talk about the vaccine to each other, share their concerns, to ensure that they can make an informed decision about getting the vaccine. In Japan, since “people around me are getting the vaccine” is one of the biggest influencers in vaccine decision making, knowing that “my friends are getting the vaccine” will be a big motivation for one to get her own vaccine.<sup>41</sup>

### **Media**

The media are undeniably one of the most influential factors in changing the publics' attitude toward the HPV vaccine and it seemed that in the Japan case, the biased media coverage has contributed largely to the HPV crisis.

Health authorities should form relationships with the media, and establish themselves as a reliable source of information. This can be firstly achieved by contacting to health journals such as Nikkei Medical or m3, and developing sound relationship with key journalists who show their interest and integrity. Provide



the journalists with the information that appeals to them, such as the shocking statistics about the burden of cervical cancers, stories about outbreaks or trend in immunization or stories about people who strongly advocate for the vaccine.<sup>49</sup>

Communicating effectively and developing a mutual understanding with other stakeholders and experts such as Japan Society of Obstetrics and Gynecologist or Japanese Primary Care Association is also crucial. When there are rising concerns about vaccine safety, a variety of stakeholders will be consulted. The conflicts in messages can result in further public's confusion. Establishing cooperation with the stakeholders, engaging them in disseminating information and developing communication plans. The consistency in messages will further enhance the credibility of information.<sup>50</sup>

### **Educate healthcare professionals about immunization and risk communication:**

Health care professionals (HCPs) play an integral part in shaping parental decisions related to HPV vaccination. Many Japanese mothers would have their daughters get the vaccine if they receive a recommendation by the family doctor, even when the MHLW had not restated its recommendation.<sup>41</sup> Especially in the situation that many concerns related to adverse events after immunization arise, doctors are the preferred, most trusted and most influential source of information.<sup>51</sup>

However, scores of studies indicated that many medical professionals do not routinely recommend the vaccine or fail to communicate effectively about the vaccine with patients and parents.<sup>51,52,53</sup> In Japan, due to the suspension of recommendation, doctors rarely recommend the vaccine, nor have sufficient basic vaccines knowledge such as vaccine's indication, interval or adverse events.<sup>54</sup>

Therefore, educating HCPs about the vaccine as well as communication skills are required to improve the vaccine coverage. We propose that:

- Creating materials such as Webinars, Education Courses, or Fact sheets to ensure that HCPs get the up-to-date knowledge regarding vaccine schedule, dosing, vaccine safety and effectiveness. The contents may be made with the collaboration of the Japan Society of Obstetrics and Gynaecology.
- Offering Communication training to physicians to ensure effective risk communication. A randomized controlled trial published in *Jama* has demonstrated the effect of Communication training in improving HPV vaccine initiation and completion, which can be used as a model<sup>55</sup>. Many Japanese mothers are worried about adverse events and they may not have the daughter vaccinated until seeing girls of similar age as their daughter get safely vaccinated.<sup>41</sup> Therefore, taking time to listen to their concerns, carefully

explaining the possible adverse events and how to deal with them, and giving examples of same-age girls who already had the vaccine is recommended.

Doctors should also express empathy when patients come to their clinics with symptoms after immunizations. Because they often show no abnormalities in the lab or imaging test, doctors at the local level usually diagnose the symptoms as “mental health problems”, or dodge responsibility by telling the patients to go visiting other institutions. Those patients then have to go many other hospitals to get the treatment, each time they get more and more tired and confused. This is the origins of many lawsuits.

Doctors should take time listen to those patients concerns, carefully explain what is known and unknown about their symptoms, and take responsibility to introduce them to institutions that can provide treatment.

## **conclusion and recommendation**

Japan is facing an unprecedented HPV vaccine crisis, and sadly the situation has lasted for 7 years. The government's withdrawal of recommendation, the biased coverage of the media, flawed study and anti-vaccine groups contribute largely to the low vaccine coverage.

Combined with the low uptake rate for cervical cancer screening<sup>56</sup>, Japanese females are being put at a higher risk of being diagnosed and dying from this disease. A modelling study published in the Lancet claimed that the vaccine crisis from 2013 to 2019 is predicted to result in an additional 24600 - 27300 cases and 5000 - 5700 deaths due to cervical cancer over the lifetime of cohorts born between 1994 and 2007, compared with the scenario in which coverage had remained at around 70% since 2013.<sup>57</sup> A recently published study in the Nature also showed that in total, number of new cases and deaths from cervical cancer among females born between fiscal year FY2000 and FY2003 (who are no longer eligible for the vaccine) will increase by 17000 and 4000, respectively, compared to the situation before the crisis.<sup>58</sup> Unless something is done about the current situation, with every passing day more and more females will lose their lives or lose their fertility due to cancer treatment.

Along with the immediate resumption of recommendation, developing an effective message by further improving the current leaflet, sharing the message by effective communication among the key stakeholders, and educating doctors is of paramount importance to improve the status quo.

Catch-up vaccination programme for those who already missed the chance during the crisis, promoting cervical screening, introducing the nine-valent vaccine, immunization for young boys should also be strongly considered for a more comprehensive vaccine programme.

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