Main challenges for scaling up HPV vaccination in Japan

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By

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Abbreviation

CC	Cervical Cancer
CRPS	Complex Regional Pain Syndrome
DALYs	Disability-adjusted life years
DPT	Diphtheria, Pertussis, and Tetanus
FDA	United States Food and Drug Administration
GACVS	Global Advisory Committee on Vaccine Safety
GAP	Gardasil Access Program
GAVI	The Global Alliance for Vaccines and Immunization
GDP	Gross Domestic Products
GSK	GlaxoSmithKline
HBM	Health Belief Model
HCW	Health Care Worker
HIC	High Income Countries
HPV	Human papillomavirus
JPY	Japanese Yen
LMIC	Low Middle Income Countries
MEXT	Ministry of Education, Culture, Sports, Science and Technology of Japan
MHLW	Ministry of Health, Labour and Welfare of Japan
MMR	Measles, Mumps, and Rubella
MSD	Merck Sharp and Dohme
NGO	Non-governmental Organizations
NIP	National Immunisation Programme
OOP	Out of pocket expenditure
Pap	Papanicolaou
PAHO	Pan American Health Organization
PATH	Program for Appropriate Technology in Health
POTS	Postural Orthostatic Tachycardia Syndrome
SAGE	Strategic Advisory Group of Experts
SHI	Social Health insurance
STI	Sexual Transmitted Infections
THE	Total Health Expenditure
TPB	Theory of Planned Model
UK	The United Kingdom
USA	The United States of America
VARRC	Vaccine Adverse Reactions Review Committee
WG	Working Group
WHO	World Health Organization
YLD	Years lived with disability
YLL	Years of life lost

Abstract

Kaori Takahashi, Japan

In June 2013, the Japanese government suspended the proactive recommendation for the HPV vaccination after several claims of adverse reactions, which raised fears for the safety of the vaccines. Even though there is a scientific consensus on the safety of HPV vaccine, the proactive recommendation has not been resumed. The position of the government is ambiguous, as the vaccine is still part of a routine vaccine and fully funded. The current low vaccination coverage (0.7% in 2014), will affect the risk of future incidence of cervical cancer.

The main objective of this literature review is to review HPV vaccine implementation failure in Japan and to explore successful strategies for implementation of HPV vaccine from other countries' cases, and use the results to formulate specific recommendations for HPV and other vaccination policy in Japan.

Even though the awareness of the HPV vaccine is high, among the target girls and their mothers, the barriers to take the vaccine remain. The vaccine hesitancy is spread to other vaccines and worldwide through sharing social media information.

To reduce the anti-vaccine sentiments, the government should make a transparent information providing system of the vaccine safety, and making use of social media. A life skill programme including vaccination and sexual education should be introduced in junior high schools. Communities and health professionals need to engage in communication with adolescents and mothers. Also, collaborating international organisations could be effective. Promoting these activities will lead to a smooth resumption and scaling up the HPV vaccination in Japan.

Key words: HPV Vaccine, Vaccine hesitancy, EPI, Implementation, Strategy

Word count: 13,194

Introduction

There has been quite an ambivalent position of the Ministry of Health, Labour and Welfare in Japan (MHLW) regarding the Human papillomavirus (HPV) vaccination. It suspended their active recommendation for routine HPV vaccination in 2013, after reports on the occurrence of some severe adverse events, attributed to the vaccine. On the other hand, as of 2017, the MHLW still supports the expenses for taking HPV vaccine, for girls of the target age, through the local governments (1,2).

Since the World Health Organization (WHO) has recommended HPV vaccination in national routine immunisation programmes in 2009, already more than 60 countries, including developing countries, have started HPV vaccination with government support (3). Even though there is global scientific consensus on the safety of the HPV vaccine, Japanese policy action is contrary to the WHO's policies of HPV vaccination. The WHO issued a statement to point out the Japanese case by name and mentioned that, without proactive recommendation, the policy leads to that young women are left vulnerable to HPV-related cancers in spite of the fact that these cancers could be prevented (4).

At the same time, MHLW promotes cervical cancer (CC) screening through local governments, to women over 20 years old, for the reason that the HPV vaccine is not 100% effective. The screening rate of CC is still low (37.7%, 20 to 69 years old in 2013) (5). This means that the women's low awareness of CC and HPV vaccine may influence the future incidence and development of CC.

While working as a consultant for the healthcare industry, I noticed that the local governments had problems to implement prevention programmes. To move people into action, a strong policy message is necessary. As a Japanese woman, I would like to contribute to finding out a possible way to overcome the challenge, of the suspended recommendation of HPV vaccination and change the policy to save women's lives. I hope this thesis can be one of the contributions that can change the policy in a positive direction towards control and prevention of future CC.

Chapter 1 Background information on Japan

1.1 Demographic information and HPV

Japan is an island country located in the northeast of Asia; the total population is about 127 million people. An ageing society (28% of the total population is over 65 years-old) is a major concern for the Japanese healthcare system (6). Life expectancy at birth of both sexes is 83.7 in 2015, and it is the longest in the world (7). At the same time, the low birth rate (1.5/1000 in 2015) has led the population to decrease; the annual population growth percentage was −0.1% in 2016 (8,9).

Among the many kinds of cancer, CC is the second biggest prevalent cancer for young women (20 to 39 years old) next to breast cancer in Japan. This cancer causes more premature deaths compared to other cancers, around 10,000 women are diagnosed, and about 3,000 women die from CC every year (10). Estimated burden of disability-adjusted life years (DALYs) of CC was 92,643, the components were 72,534 years of life lost (YLL) and 20,109 years lived with disability (YLD) in 2008 of women of Japan (11). The death from CC was around 2% of all cancer deaths in women (12). The age-standardized mortality rate of CC is 2.8 per 100,000 women per year (estimated for 2012), this rate is relatively low compared worldwide; 6.8 per 100,000 women per year (13). The age-standardized incidence rate (estimated) is 10.9 per 100,000 person-years in 2012, and this incidence rate is higher than other developed countries; 6.6 per 100,000 person-years in the United States of America (USA), 7.9 per 100,000 person-years in Eastern Asian countries, and 14.0 per 100,000 person-years worldwide (11,12). Though this rate in Japan is still moderate, the trend of prevalence, in young and middle age (15 to 39 years old), has significantly increased in 10 years; 26.4 per 100,000 women in 2002 to 87.0 per 100,000 women in 2012 (14).

HPV is known as the cause of most CC, and it is sexually transmitted. Though there are more than 100 types of HPV, the types which develop CC are called "high-risk HPV" and especially particularly subtypes 16 and 18 which are known as high-risk HPV causing up to 70% of the whole burden of CC. More than 50% of women, who are sexually active, are said to be infected with HPV once in their lifetime, but even though infected, most of them do not develop CC. About 90% of the HPV infections are cleared up within two years. The HPV vaccine expects to prevent infection of this two high-risk HPV (16 and 18), and two types of vaccines are available which are Cervarix® and Gardasil® in Japan (10).

1.2 Socio-economic situation

Japan is classified as a high-income country (HIC) in the World Bank classifications. Gross Domestic Products (GDP) of Japan was 4.94 trillion USD in 2016, it took the third place in the world, with a growth rate of GDP of 1.0% in 2016. GDP per capita in 2016 was 38,895 USD (9). According to WHO, the total health expenditure (THE) percentage of GDP in 2014 was 10.2%, and the 'THE' per capita was 3,703 USD in the same year. Compared to the worldwide (1,059 USD in 2014), the expenditure level is high. Though the medical demand is expected to grow with the ageing society, on the other hand, the government moves to restrain medical expenses because the social health insurance pooling is expected to decrease with the decline of the productive population (15). Out of pocket expenditure (OOP) as the percentage of THE was 14% in 2014, but in the health system, 30% of medical expense is required to pay as a user fee by aged 6 to 69 years old. For the people of other ages (children and elder people) are applied to pay only 10% or 20% of the fee. Because most of the people who use medical services are elderly, OOP/THE is averaged to 14%. From 2014, seniors with a high-income are required to pay the 30% of the user fee due to the medical expense change by MHLW; the OOP rate is expected to increase (15).

1.3 Health system

1.3.1 Social health insurance system

Japan has implemented a mandatory social health insurance (SHI), which is a combination of contributions collected from employers, or from local governments (in a case of self-employed and unemployment). Although all citizens are covered by any insurance system, the payment for medical service is the same price, regardless of health institutions or insurances, as long as the treatment is covered by the SHI reimbursement. The medical fee is decided by MHLW and people can receive necessary medical service by paying 30% of the total expense at the reception (except for children and elderly people). There are no restrictions on access to care, but only when people go to big medical institutions, such as university hospitals without a referral letter, an additional consultation fee of 5,000 of Japanese Yen (JPY) (around 50 USD) is required as of 2016. As general practitioners also have expertise, patients can choose clinics and hospitals according to symptoms. Health facilities tend to orient treatment to acquire a higher health insurance reimbursement, and doctors have no incentives nor responsibility to guarantee continuity of care of particular patients (16).

The medical insurance reimbursement price is set and changed every two years by MHLW. The trend of medical insurance reimbursement price setting has been reducing to suppress the increase of total health expenses. Most of the health insurers, especially local government insurers, which cover self-employed and unemployment persons, are deficit and supported by tax; about 7% of the total health expenditure is supported by tax in 2014 (17).

Usually, health promotional activities such as health education, vaccination, regular check-up and cancer screenings are not included in SHI reimbursement coverage. Instead, local governments have the responsibility to pay for those activities. Immunisations are free, due to the compensation programs by the local governments, as long as they are part of routine vaccines. Though MHLW has a general policy at the minimum level, the target groups for the vaccines are expanded depending on each district, depending on the financial situation of the district. For example, the Edogawa district government, the Tokyo Prefecture supports the HPV vaccine expense partially for girls with age of 20 (18). Also, some insurers (most of the time employers) have their health promotion programs, such as a comprehensive medical survey and compensation of the influenza vaccination fee; influenza vaccines are not supported by the government, so people have to pay the user fee (OOP) (19). Haemophilus influenza type B (Hib), Pneumococcal, Hepatitis B, Diphtheria, Pertussis, Tetanus (DPT), Polio, BCG, Measles, Rubella, Varicella, Japanese Encephalitis and HPV are implemented as a routine vaccine through the National Immunisation Programme (NIP) of 2017 (20). All vaccines are officially recommended except for HPV vaccine. Meanwhile, mumps and rotavirus vaccines have not been introduced in the routine schedule in Japan, even though they are recommended by WHO (21,22).

1.3.2 Control and prevention of CC

There is a cancer screening Papanicolaou (Pap) smear test and HPV vaccination program which expense is supported by local governments. The screening test is managed by local governments as a cancer screening program, and the compensation programs are different each district. Although governments have offered a free CC screening coupon to women at the ages of every five years from 20, 25, 30, 35, and 40, the screening rate was 37.7% (20 to 69 years old) in 2013. The rate was about half compared to other developed countries (5). Increasing the screening rate is one of the important issues for local governments. Recently, there is an increased case of discovery of CC during the CC screening in the initial pregnancy check-up (23).

The HPV vaccination program by local governments has been implemented in December 2010

after the licensing of vaccines, and became a routine vaccine in April 2013. However, in June 2013, the MHLW suspended the proactive recommendation for the HPV vaccination until the issue of the safety of the HPV vaccine was solved. Still local governments continued to provide the HPV vaccination at the applicants' request from girls that target ages from 12-16 years old. Because of the lack of health promotion by local governments, the vaccination rate is extremely low (0.7% in 2014) (24). There is no national data for the vaccine coverage rate, but before the government suspension of recommendations in 2013, the HPV vaccination rate was around 70% for the completion in Sapporo city in Hokkaido, dropped to 0.6% (25). The rate in Sakai city in Osaka fell from 70-80% to 3.9% (26).

1.3.3 Policy tendency

Japanese parliamentarians are elected by the general citizens, the general election and the ruling party elects the Prime Minister. Since the Prime Minister chooses each minister, each ministries policy is directly linked to the policies of the ruling party (27). Japanese news agencies have been widely trusted historically; it is thought that the information from the media significantly affects elections and national policies (28).

The terms of the policy of vaccine implementation are discussed and decided by the council of MHLW. The council consists of researchers, medical provider organizations, and academic stakeholders (29).

Chapter 2 Problem statement and justification

2.1 Problem statement

In June 2013, MHLW suspended the proactive recommendation for the HPV vaccination after several claims of adverse reactions were broadcasted, which raised fears for the safety of HPV vaccines. MHLW reported that the suspension would last until the frequency of occurrence of side effects had become clear, and they would be able to provide appropriate information (2). At the same time, the MHLW continued to provide the HPV vaccine for free for target aged girls (12-16 years old) as the NIP, without any promotional activities (1,2,10). Specialist associations such as the Japan Society of Obstetrics and Gynaecology requested the restart of the proactive recommendation of HPV vaccines in August 2015 (30); also, the WHO declared the HPV vaccine to be safe; however, as of July 2017, the suspension of the HPV vaccination recommendation continues (31). Even though the safety was carefully confirmed, before the implementation of the routine vaccine, MHLW easily stopped proactive recommendation, and it has been taking a long time to resume. Gilmour et al. (21) mentioned that since the present system of reporting the adverse events does not follow a systematic process to identify the cause, a strict and scientific approach is necessary to investigate adverse events which are related to HPV vaccines.

The suspension of the recommendation of the vaccination means that the government does not promote any activities for the targets such as sending postcards, informing through posters in health institutions and conducting vaccination in schools. It may easily lead to that girls and parents miss vaccination opportunities. Combined with the anxiety for the vaccine, the vaccination implementation rate of HPV vaccine, which was originally low at 17.2% in 2013 further dropped to 0.7% in 2014 (24). Statistics on the coverage rate of HPV vaccine does not exist before 2013; that was the first year the vaccine was included to NIP. Until then the vaccine was only partly supported by the local governments, so the vaccinate rate was not thought to be high. In Japan, HPV vaccination has never succeeded. It is thought that the target age girls are exposed to the risk of future incidence of CC even though the infection of HPV is preventable. The sexual behaviour of adolescents has changed, and the age of sexual debut is more early. According to a national survey in 2011, 304 (24%) on 1,289 female high school students (16–18 years old) reported sexual experiences, whereas the proportion was only 9% in 1981 (12). When the age of sexual intercourse becomes earlier, the number of the lifetime sexual partners will increase, and it may lead to higher HPV infection rates.

Meanwhile, the anti-HPV vaccine groups' activities continued in Japan, in February 2017, the victim's group requested compensation for damages of the Japanese government, GlaxoSmithKline (GSK) and Merck Sharp and Dohme (MSD) in a lawsuit at Tokyo District Court, and the two companies and the government were seeking dismissal of claims (32). The anti-vaccine movement can be seen worldwide; the movement is not only spread to low middle income countries (LMIC) but also to a high educated and well-informed group in HIC (33). An analysis for HPV vaccination through YouTube turned out that even it was the minority, but 25.3% of the videos expressed the vaccination negatively (34). Not only HIC but also lots of LMIC overcame this anti-vaccine sentiment and achieved a high HPV vaccination rate. The successful policy making and implementation strategies of the HPV vaccine in other countries could be helpful for Japan's case to restart a proactive recommendation of HPV vaccination.

2.2 Justification

Clarifying the individual and contextual factors of Japan, that constitute barriers for scaling up the HPV vaccines in the NIP, will contribute to reducing future incidence and prevalence of CC due to HPV. Moreover, to clarify the success strategy of an introduction and scaling up of new vaccines will contribute greatly to public health problems regarding prevention of infectious diseases. Since the topic is increasingly debated in the whole western world,

learning from other countries' cases will be a hint for restarting the recommendation for the HPV vaccination by the MHLW.

2.3 Research questions

This thesis will answer the following research questions:

1. What were the factors that made MHLW decide to stop the HPV vaccination recommendation?
2. What is the perception of HPV vaccination and its uptake/coverage in Japan?
3. What is the relevance of anti-sentiments for HPV vaccine in HIC and LMIC for the situation in Japan?
4. How other countries including LMIC deal with and handle anti-vaccine movements toward HPV vaccination?

2.4 Objectives

2.4.1 Main objective

To review HPV vaccine implementation failure in Japan and to explore successful strategies for implementation of HPV vaccine from other countries' cases, and use the results to formulate specific recommendations for HPV vaccination policy in Japan.

2.4.2 Specific objectives

1. To review the policy implementation of withdrawal of proactive recommendation for HPV vaccination that MHLW made.
2. To explore the perceptions on HPV vaccination leading to its uptake/coverage in Japan.
3. To explore the relevance of anti-vaccine sentiments for HPV vaccine in HIC and LMIC for the situation in Japan.
4. To review the literature on successful strategies to handle anti-vaccine movements towards the implementation of HPV vaccination as a routine vaccine from a worldwide perspective including LMIC.
5. To formulate general recommendations that can be adopted to HPV vaccination re-recommendation in Japan from other countries' strategies.

2.5 Methodology

2.5.1 Search strategies

This study is based on literature review. Literatures were searched from VU library, PubMed, Cochrane Library, CiNii (a database which can search Japanese academic literature) and the search engine of Google Scholar. Grey literature such as policy and reports, documents from MHLW, WHO, other national and international organisations, and Non-governmental organizations (NGO) were also reviewed. The key words were searched separately and in combination (Table 1) to capture the many expressions of perceptions/sentiments and national policy for HPV vaccine implementation. The keywords of the search strategy were used in both Japanese and English.

2.5.2 Inclusion and exclusion criteria

Inclusion criteria were based on the relevance to the perceptions of HPV immunisation, the news or reports on impacts of HPV vaccines, immunisation policy, and international vaccine implementation practices as a NIP after HPV vaccines licensed. This literature search included both quantitative and qualitative studies. However, articles were excluded if the research was only clinical, such as describing the effectiveness of HPV vaccine to prevent CC. After the search terms had been retrieved, the articles were screened by title and abstract following a combination of inclusion and exclusion criteria.

2.6 Study limitation

There was a language bias in this review, since only literature written in English and Japanese was reviewed. As not all literature could be accessed, because of the license, findings could be limited. Since most of the studies about Japanese perceptions for HPV vaccines were practised by districts, the findings might have a bias by the population group. HPV vaccine is relatively newly introduced as a routine vaccination to Japan, and there is still a discussion of the recommendation suspension of the vaccine, this literature review is limited to those by 2017. In addition, because of the limitation of time, there might be a selection bias.

2.7 Analytical Framework

The framework "Model of determinants of vaccine hesitancy" was developed by the Strategic Advisory Group of Experts Working Group (SAGE WG) (35) (Figure 1) (36) and was used to investigate the objective 2) explore the perceptions on HPV vaccine uptake in Japan. According to SAGE WG, "*vaccine hesitancy*" was defined as "*a behavior, influenced by a number of factors including issues of confidence (do not trust vaccine or provider), complacency (do not perceive a need for a vaccine, do not value the vaccine), and convenience (access)"* (37). The framework was developed for dealing with general vaccine hesitancy and not particularly analysis for the hesitancy of HPV vaccine. However, HPV vaccine is a comparably new vaccine that many countries are still introducing, though the HPV vaccine has a particular target group and characteristics that relate to the sexual nature of transmission of HPV, the analysis of the perception through this framework was judged useful.

The framework describes three main domains; 1) Contextual influences, 2) Individual and social group influences, 3) Vaccine and vaccination-specific issues, and this model includes the identifying of potential influencers. Well known psychological models to analyse behaviours and perceptions such as Theory of Planned Model (TPB) and Health Belief Model (HBM) focus on individual perception. A Socio-Ecological Model is usually used for the analysis of the interaction of individuals, relationships, community and social factors. The framework "Model of determinants of vaccine hesitancy" is superior to others regarding being developed specifically to analyse both individual perception and social/contextual influence.

Table 1. Key words used in search literature

HPV		uptake	behavior	trust	policy	mother	Japan
		cervical	belief	culture	implement	child	low income
		risk	accept	sentiment	strategy	girl	middle income
vaccine	AND	attitude	fear	anti	sexual	adolescent	coverage
		barrier	concern	hesitancy	provider	school	program
		perception	anxiety	adverse	recommend	education	cost
immunization		awareness	side effect	routine	physician	knowledge	influence

Figure 1. The SAGE Working Group "Model of determinants of vaccine hesitancy"

Source: SAGE WG (2014) (36)

Chapter 3 The policy the implementation of the withdrawal of proactive recommendation for HPV vaccination in Japan

This chapter reviews the MHLW policy implementation before and after it suspended a proactive recommendation for HPV vaccination. Details on the timeline are shown in Table 2.

3.1 After HPV vaccines were licensed (From 2009 to April 2013)

There are two HPV vaccines which were licensed in Japan, Cervarix® in 2009, and Gardasil® in 2011. In the beginning, the local government support for HPV vaccination started from 2009 after licensing Cervarix®, then the expenses for Cervarix® vaccination was partly or fully supported by the national fund from 2010 (2). The support program for implementation of the HPV vaccination, varied across local governments, by April 2010, 126 local governments decided to start financial support program for the vaccine. The financial support for Gardasil® started from September 2011 (1). From April 2013, the HPV vaccine introduced as a routine vaccine, the expense for the vaccine has been fully supported by the government (2). Though there is no national survey of the vaccination rate of the HPV vaccines before 2013, originally the price of HPV vaccine was high, and due to the OOP burden of adolescents and family, the vaccination rate was thought to be low.

MHLW has gathered side effect reports since the Cervarix® was licensed. However, the side effect reporting system required to report just all the reactions after vaccination, regardless of the causal relationship with the vaccination or not. As of February 2011, cases of side reactions such as fainting and anaphylactic shock were reported, but the possibility of those side reactions after the Cervarix® vaccination was reported from the GSK in advance (38).

After a news from Asahi newspaper, about the severe cases of side effects after taking HPV vaccination in March 2013, the trend for HPV related news changed negatively. The end of the month, after the press conference of the "victim group" of HPV vaccination, the side effects of HPV vaccines especially severe side effects such as anaphylactic shock and complex regional pain syndrome (CRPS), have become widely known in Japan (1). The YouTube video of the girls suffering from severe side effects such as seizures and walking disturbances, were spread on Japanese social media mainly in 2013 and 2014 (1).

3.2 During the HPV vaccines being proactive recommended as a routine vaccine (From April to June 2013)

In April 2013, the NIP included HPV vaccines. In the same month, Suginami (district of Tokyo) local government announced the compensation for the girls who were suspected with CRPS after HPV vaccination (1). The anti-vaccine movement for HPV vaccine continued after the vaccine scheduled as a routine vaccine, the responsibility of the national government, for the side effects of vaccination, had started to claim. Also, in May 2013, several members of the committee, who participated the introduction of the HPV vaccine, turned out that they received money from MSD or GSK. This fed a conspiracy theory, about a political adhesion between the government and the pharmaceutical companies regarding vaccine introduction (29).

The WHO Global Advisory Committee on Vaccine Safety (GACVS) (39) reported the safety and necessity of the HPV vaccination referring to the Japanese case, on 13 June 2013, however, the announcement was not widely reported through Japanese media, and the next day, on 14 June 2013, MHLW decided the suspension of a proactive recommendation of the HPV vaccine (1).

3.3 After the proactive recommendation for the HPV vaccination was suspended (After June 2013 to present)

After the suspension of the proactive recommendation by MHLW, the HPV vaccines continue in the routine vaccination schedule until today. The kind of ambiguous approach was decided by the council for vaccines because "HPV vaccine safety is unclear, but it is not necessary to remove it from a routine vaccine schedule, considering the private expense of the vaccine is expensive" (29). The government strengthened the compensation program for the girls, who had side effects after HPV vaccination. MHLW set the information page about the HPV vaccine program like Question and Answer (2). In August 2015, a clinical practice guideline corresponding to the abnormal reaction after HPV vaccination was published by the MHLW.

The policy stance of MHLW is that the suspension of the recommendation of HPV vaccine would continue until the causation of the adverse reactions after the vaccination and the safety of the HPV vaccine was clarified. The cause of adverse reactions has been reviewed by the Vaccine Adverse Reactions Review Committee (VARRC) of MHLW (29). In January 2014, the VARRC of MHLW concluded that there was no evidence of a causal association between the HPV vaccine and the reported adverse reaction and also reported the side reactions cases after HPV vaccinations were not more frequent compared to other countries, but MHLW did not resume proactive recommendations for HPV vaccines (25,29). Additionally, in July 2014, the VARRC continued the same conclusion of January 2014 and regarded the chronic pains as "functional physical symptoms", however, the idea was not understood commonly and did not lead to the resumption of the proactive recommendation. In December 2016, the result of a national epidemiological survey reported that causal relationship between HPV vaccination and the symptoms that occurred after HPV vaccination cannot be established. In April 2017, additional research of the national epidemiological survey was conducted and supported the previous result (29).

Opinions of experts on HPV vaccination vary. A symposium held by the Japan Medical Association and Japanese Association of Medical Sciences, argued the statement that HPV vaccines should be scaled up, after the issues regarding vaccine safety, were settled in December 2014. The proposal of a new syndrome of "HPV Vaccination Associated with Neuropathic Syndrome (HANS)" was introduced by one doctor at the symposium. He named the relevant pain symptoms for vaccine takers as "HANS", but no scientific research has been conducted (1).

MHLW asked the two professional groups to investigate the relationship between adverse reactions and the HPV vaccine. In March 2016, one group reported that HPV vaccine had a possibility to cause autoimmune diseases. But later, the research report was turned out to be inappropriate, because the data was only from one mouse injected with HPV vaccine (40). It added an argument to the confusion.

Experts groups who were concerned about the situation, exposed future CC prevalence, had issued statements that required restarting of the proactive recommendation of HPV vaccination by MHLW. In August 2015, the Japan Society of Obstetrics and Gynecology requested to restart the proactive recommendation of the HPV vaccine (30), following that, in December 2015, WHO GACVS stated the safety of HPV vaccines again and strongly recommended to introduce the vaccines into the NIP. In this report, the WHO pointed out the Japanese case that the policy making, based on weak evidence and lack of using safe vaccine, could lead to real harm in the future (4). In April 2016, 17 specialists' groups including the Japan Pediatric Society and Japan Society of Obstetrics and Gynecology, issued the statement for the resumption of the HPV vaccine recommendation (41).

Anti-HPV vaccine groups have acted continuously, they sometimes protested in front of the building of two pharmaceutical companies and the demonstrations were broadcasted (1). In July 2016, 63 girls who had severe side effects of HPV vaccines announced to file lawsuits for four districts courts (Tokyo, Nagoya, Osaka and Fukuoka) for the request of compensation for side effects (41). Against the announcement, GSK and MSD made a statement for the HPV vaccine safety (42,43). In February 2017, the victim's group requested compensation for side effects and serious damages from the Japanese government, GSK and MSD in a lawsuit at Tokyo District Court, but the three accused were dismissed of claims (32).

Table 2. Events related to HPV vaccine implementation

Time	Governmental actions	Supportive actions	Adverse actions
October 2009	Cervarix® licensed		
April 2010	The support program started for HPV vaccine started		
October 2010	Central and all local governments launched a temporary funding program		
February 2011	MHLW reported the gathered side effect cases after vaccination		
September 2011	The financial support for Gardasil® started		
March 8 2013			Asahi newspaper reported that 50 girls suffered from CRPS and 100 were absent from school after taking HPV vaccine, the negative report videos spread online
March 25 2013			Press conference by the victim group of HPV vaccine side effects was reported, the video remains on YouTube
April 1 2013	HPV vaccines were implemented as a routine vaccine		
April 13 2013	Suginami local government decided to compensate for the girls who were suspected CRPS after HPV vaccination		
May 9 2013			Another press conference by the victim group reported
May 16 2013	MHLW revealed that some committee members of HPV vaccine received money from GSK and MSD		
June 13 2013		WHO announced the safety of the HPV Vaccines	
June 14 2013	MHLW suspend proactive recommendation of HPV vaccine		
January 2014	MHLW concluded that there was no evidence of a causal association between the HPV vaccine and adverse reaction		

Time	Governmental actions	Supportive actions	Adverse actions
July 2014	MHLW VARRC concluded that there was no evidence of side effects of HPV vaccine again		
October 2014			National Cervical Cancer Vaccine Victim Liaison Committee launched
December 2014			Symposium held by Japan Medical Association argued that HPV vaccines should be scaled up after the issues regarding vaccine safety were settled "HANS" introduced
March 2015			Anti-vaccination groups protested in front of the buildings of MSD and GSK, which is broadcasted
August 19 2015	The clinical practice guideline for the reaction after HPV vaccination published		
August 29 2015		Japan Society of Obstetrics and Gynecology requested to restart proactive recommendation of HPV vaccine	
December 17 2015		WHO announced the safety of the HPV Vaccines again	
March 16 2016			One research group reported inappropriate research result that there was a relationship between HPV vaccine and cause of autoimmune diseases
April 18 2016		17 specialists' associations stated the request for resumption of HPV vaccine recommendation	
July 27 2016			The victim group announced to filed lawsuits for 4 districts (Tokyo, Nagoya, Osaka and Fukuoka) for the request of compensation for side effects, The news was widely featured
July 27 2016		GSK issued the statement for the safety of HPV vaccine	
September 28 2016		MSD issued the statement for the safety of HPV vaccine	
December 26 2016	The result of a national epidemiological survey showed that relationship between the adverse reaction and HPV vaccination cannot be explained		
February 2017			The victim group filed a lawsuit at Tokyo District Court toward GSK, MSD and Japanese government but the three-accused rejected the lawsuit
April 10 2017	Additional epidemiological research conducted and supported the previous result		

Source: Modified from Wilson et al. (2015)(1); documents of MHLW (29)

3.4 Discussion

The MHLW seems concerned that Japan lags behind the world, with regard to scaling up the HPV vaccination and furthermore the WHO accused Japan by name. To restart the recommendation, the MHLW has been investigating the safety of the HPV vaccine and the relationship between adverse reactions after vaccination and the HPV vaccine. There are various opinions about the vaccination among the specialists and VARRC committee members, MHLW seemed to have missed the chance to change the policy. Even though it seems important to promote wider opinions, on the effectiveness and safety of the HPV vaccine by the committee, in spite of CC being a specialised area of gynaecology, it was questionable that no gynaecologist attended the committee.

Although the possibility, that some cases of adverse reactions such as anaphylactic shock had been confirmed by the MHLW before the introduction of HPV vaccines, in addition, the incidence of the side effects is not particularly high in Japan, the media reported it as if the vaccine itself is dangerous. The fact that some committee members received money from pharmaceutical companies, even though the money was a legitimate remuneration, seemed to accelerate the anti-vaccine movement.

According to Ozawa and Iwanari (44), this was the fifth time that MHLW suddenly stopped a vaccination; the stop of the recommendation for vaccinations was DPT in 1975, measles, mumps, and rubella (MMR) in 1993, Japanese Encephalitis in 2005, Hib in 2011, and HPV in 2013. As for the previous cases, every vaccination resumed as a routine vaccine except the vaccine for mumps. The suspension of the vaccines uptake recommendation, without scientific investigation by the committee, seemed to be affected by the lack of fundamental organisations which promote vaccine scaling up.

To sum up, vaccine implementation policies should be carefully reviewed for the main concern of future prevention of the target disease and not just react to claims of possible adverse events. Risks and benefits should be debated transparently as a prerequisite of the occurrence of a certain degree of adverse effects in any vaccine. Then, MHLW should develop a comprehensive and fundamental policy and organisation for the implementation of vaccines. The vaccine council should be designed to promote the introduction and review the progress regardless of the type of vaccines, avoid conflicts of interest of committee members, collect data on side reactions from the trial stage through the cooperation with pharmaceutical companies and medical institutions and promote international exchange with similar public health institutions abroad on these issues.

Chapter 4 The perceptions of HPV vaccination leading to its uptake/coverage in Japan

This chapter analyses the perceptions on HPV vaccination leading to its uptake/coverage in Japan through using the framework of SAGE WG "Model of determinants of vaccine hesitancy" (Figure 1) (36).

4.1 Contextual influences

4.1.1 Communication and media environment

The mass media acted negatively about the civilian perception and the HPV vaccine coverage rate. One research (45) showed that after hearing the negative reports, 29% out of 2,777 study participants who already finished at least a first dose decided to stop taking HPV vaccination. The problem is that the media reports were not so objective, and rather amplified the voice of the girls who had serious adverse reactions and unfortunately developed difficult to treat disorders after the HPV vaccinations (25). Ropeik (46) highlighted that the news media emphasised the characteristics of the risks which more likely drew people's attention and alarm for the vaccine risks. According to Dubé et al. (47), the features of online information was that they distributed faster and larger anti-vaccination sentiments. The information on Internet was often catchy, anecdotal and readable but without presenting any scientific information. What made matters worse, the diffusion of contents was outside the attention of the scientific community.

In addition, the ambiguous reaction of the combination of the negative news of side effects and MHLW halting the proactive recommendation, fed fears of the target age girls and their parents about the HPV vaccine (48). The announcement of MHLW had less power than the news of severe adverse reactions. The MHLW and experts should have been more active exposing to media to correct information widely (48). Moreover, Okuhara et al. (49) explained the readability of the online message of pro-HPV vaccination mostly written by experts were more difficult than anti-HPV vaccines messages. Generally, narrative reports of adverse events are more easy to read for people compared to reading the scientific and statistical safety of the vaccine. Easy-to-read reports easier lead to creating trust.

4.1.2 Influential leaders and individuals

It seemed that the victims and the doctor advocating CRPS could influence vaccine hesitancy through media. On the other hand, there was little literature found that had a positive impact. The declaration of GACVS, the WHO was seemingly not enough to handle the fears about adverse HPV vaccine reactions of the general population (50). In the United Kingdom (UK), there was a "positive" event that was called the "Jade Goody effect" in 2009, which was after the death of the female reality television star from CC at the age of 27, the number of the screening test increased (51). However, this effect appeared to have little impact in the Japanese case.

4.1.3 Historical influences

Anti-vaccine sentiments did not to begin recently. According to Poland (52), there was an anti-vaccine movement for the pertussis vaccines, and the concerns prevailed worldwide including Japan (Sweden, UK, Soviet Union, Italy, former West Germany, Ireland, Australia and Japan) during the 1970s.

Historically, the Japanese government had excluded some vaccines from routine vaccination programs because of the adverse events without enough scientific evidence. For instance, the MMR vaccines were excluded from routine vaccines in 1993 because of the incidence of meningitis but rescheduled again in 2006 without the mumps vaccine. Nowadays, mumps vaccine can be taken with the personal expense (some local governments support partly) as

an optional inoculation vaccine (44). When the HPV vaccines were suspended off the recommendation, the causation between the HPV vaccines and the adverse reaction was not found, nor any scientific research had been conducted. On the other hand, Hib vaccine and Pneumococcal vaccine are regarded that were implemented to a routine vaccine without adequate risk assessments by MHLW (21). In this way, there is a high possibility that insufficient risk assessments to a routine vaccine and the action to halt the vaccination immediately after the adverse reactions by MHLW have widely announced, have led to distrust of people.

4.1.4 Religion/Culture/Gender/Socio-economic

4.1.4.1 Religion

Japanese major religions are Shinto and Buddhism (53). One research (54) mentioned that both religions are not interfering with vaccination.

4.1.4.2 Culture

Japanese people tend to hesitate to talk about sexual issues among the family, particularly between parent and child, so that there is a lack of cultural factors that are able to sexual explanations related to CC and HPV within a family, for the girls who became the age of receiving HPV vaccines (55). Discussions on sexual issues among policy makers also seem to be tabooed, previously, the low-dose oral contraceptives introduction to Japan, had not been approved until 1999, it delayed 40 years after the first introduction in the USA in 1960. Part of the reasons for the approval delay was that concern about the side effects and the increase the spread of Sexual Transmitted Infections (STI) without using condoms (56). Both abortion and contraception are approved but not covered by SHI reimbursement.

4.1.4.3 Gender

From the research analysis of perceptions of males about HPV infection and CC (57), there was the idea that a single father had the difficulty to take their teenage daughter to a gynecologist because generally there is no male in the clinics or healthcare institutions of gynecology. Another idea from the research was that it was difficult for a father to talk about sexual issues to daughters at home.

4.1.4.4 Socio-economic

Larson et al. (33) identified that at a global level, the level of income status was a significant vaccine acceptance factor. Little literature mentioned the relevance with the Japanese HPV vaccine acceptance and socio-economic status. One study (58) of the rural area (Aomori Prefecture) discovered that there was a significant difference among mothers' occupations and their level of knowledge of HPV vaccines. When the mother was medical staff or teacher, she had a higher level of knowledge than other occupations. Regarding the cost of HPV vaccines for out of the target age, it would become a barrier factor. However, there was little literature found that the socioeconomic status was a significant factor which improves or constraints HPV vaccination in Japanese case. On the other hand, regarding the educational level, the lack of knowledge of HPV and CC was found at any level of the educational system of Japan, no matter what levels of schools their parents graduated (57).

4.1.5 Politics/policies (mandates)

Even though the HPV vaccination is scheduled as a routine vaccine, the vaccination is not mandatory for the girls. Girls and mothers have the option not to take HPV vaccines. The articles which mentioned the hesitancy of Japanese about mandatory vaccination were not found. Regarding the HPV vaccines, the discussion on mandatory vaccination has not taken by the government. Conversely, according to Yuji and Nakada (59), the suspension of the recommendation for HPV vaccination by MHLW in 2013 rather fed the doubt among the public and HPV vaccination coverage remained low. Historically, the government implemented mandatory immunisation of some vaccines for school children, in 1994 it ended because of the public pressure that people should decide for the vaccination. Since the herd immunisation

system weakened, occasional outbreaks of measles occurred in 2006 (60). Though it is not regulated, elementary schools often require children to be vaccinated before admission conventionally.

4.1.6 Geographic barriers

From the survey of Hanley et al. (61), more than half of the mothers of girls 11–14 years old, answered they would choose small neighbourhood clinics or schools to give HPV vaccination for their children. The research conducted in 2012, after the HPV vaccines became a routine vaccine in 2013, only medical institutions have been allowed to provide the vaccine. In the present circumstances, as of July 2017, generally, there is a necessity the mother takes her children to health care institutions. Depending on the availability of the institutions, children have to be absent from school. Fujiwara et al. (62) recommended that school vaccination of target grade girls was effective for raising the HPV immunisation rate through experience, that one rural city tried vaccination for the 6th-grade girls and succeeded in a high vaccination rate (98.8%) at the districts, before HPV vaccines became a routine vaccine.

4.1.7 Pharmaceutical Industry

As mentioned in previous sections, there was a conflict of interest among the committee members of vaccines in MLHW and pharmaceutical companies (29). Although the conspicuous activities such as lobbying by the pharmaceutical companies could not be seen, since the HPV vaccine was initially high price, the committee members were doubted to move for the interest. Nakada et al. (51) referred the possibility that GSK and MSD might have indirectly promoted HPV vaccines through the patient's groups of CC or NGO with donations to them. If it is revealed to be true, the hesitation perception level would increase. After the adverse reactions had been reported, the pharmaceutical companies and the drug regulatory agencies were asked to submit the data of the clinical trial. However, they explained the medical records were coded in the process, and the raw data was lost. This series of coding was regarded by people as information hiding (63). Ropeik (46) mentioned the public hesitancy for vaccines often relates to intentions of the high-profit industry.

4.2 Individual/social group influences

4.2.1 Experience with past vaccination

There is little literature that researched the relationship between the experience of past vaccination and hesitancy. Hattori et al. (64) showed in their research that the students who did not yet have a first HPV vaccination had more concerns about the side effects and the pain of intramuscular injection, compared to the students who experienced HPV vaccines at least one time of the three. Even a girl who experienced HPV vaccines without knowing the intramuscular injection reported that she hesitated for the second and subsequent vaccinations because of the severe pain of the injection (65).

4.2.2 Beliefs, attitudes and motivation about health and prevention

The literature related attitudes and motivation toward HPV vaccination were mainly found from mothers of the target age daughters. The research of Hanley et al. (61) showed that the attitude of Japanese mothers for HPV vaccination for their daughters is mostly positive especially in the case that physicians clearly explain the risk, safety, and the necessity to take vaccines for the girls of the target age. Several studies also showed (61,66) the mother’s motivation, whether let her daughter take an injection depends on the mother’s experience of regular screening. All the mothers of the research who had been infected by HPV or diagnosed as CC answered that they would let their daughters’ take HPV vaccination. On the other hand, another study (26) mentioned the Japanese mothers did not usually make a decision by themselves and ask others their ideas. The literature concluded it was difficult to change the attitudes of such mothers even if they were educated on the matter. In this

research, the mothers' attitude was described that the policy change, that MHLW resumes the proactive recommendation of HPV vaccines, would not be enough for the mothers to change their mind to let their daughters take the vaccine.

Besides, HPV vaccination requires explaining about how HPV infect, which is by sexual intercourse. Though there was a rumour that HPV vaccination would make the girls sexually active, Larson et al. (45) refused the rumour as a result of the investigation.

4.2.3 Knowledge/awareness of vaccines

From the various researches (65,67,68) conducted that most of the girls had knowledge and awareness of CC and HPV vaccines. However, the majority of them overvalued that the vaccines could prevent CC in 80 to 100% (actually the prevention rate was about 70%) (65). The process that the girls would uptake HPV vaccines, that the most of the girls got information on CC and the HPV vaccination from the documents from school which were distributed by experts, or from the communication with local healthcare experts, parents and friends (65).

There is often the case that the decision maker of the vaccination is the mother. Several researches have shown (61,69) that around half of the mothers, who had adolescent girls, had heard of HPV and believed that their daughter had a chance to be infected by HPV within her lifetime. Though that was a correct understanding, they misunderstood rather worse that HPV infection meant great risk for developing CC; as if all types of HPV develop CC. A survey (69) of the girls in 7th grade (12 or 13 years old) and their mothers described that most trustworthy information sources for the mothers of the CC screening and HPV vaccination were doctors and media (newspapers/television).

4.2.4 Personal experience with and trust in health system and provider

Several researches (48,69) showed that the mothers of adolescent girls, regarded physicians as a reliable information resource, and tended to be influenced from the recommendation for preventive services by the doctors. Yet, Ito et al. (69) mentioned that the environment of the Japanese CC screening test lacked the privacy; often the voice conversation of the examination room leaks outside and many nurses walk aside during the screening. Patients were not able to control the environment. It might become a negative image for mothers for CC screening and lead to the decision making not to take HPV vaccination for their daughters.

4.2.5 Risk/Benefits (perceived/heuristics)

Ropeik (46) explained that the fear for vaccines to children is much greater than for vaccines targeting adults. People tend to take the vaccine risks more seriously than their benefits because the benefit of preventing diseases in the future is invisible compared to the risks of the side effects immediately after the injection (46). Yagi et al. (26) also described, not only the risk of side effects but also the benefits of HPV vaccines are considered when girls decide to take the vaccines. In addition, the mothers were concerned about the HPV vaccine efficacy and fears at the same time (61).

4.2.6 The norm of immunisation

Several literatures (26,65) mentioned that the encouragement for HPV vaccines from girls' friends was a significant positive factor, for increasing the motivation to take HPV vaccines. It would be a peer pressure for the girls and persuade their mothers who were sceptical for the vaccine. Hearing from friends about the pain level of the intramuscular injection and adverse events occurred after the injection was effective to make the girls feel relieved about the side effects of the vaccine (65).

4.3 Vaccine and vaccination-specific issues

4.3.1 Risk/benefit (scientifically based)

As for the scientific risk and benefit, VARRC of MHLW reported that the frequency of the severe adverse reactions after HPV vaccination was not especially high compared to other countries considering the difference in the reporting system. Also, the committee reported that most of the severe cases after the vaccination disappeared or were relieved within the several months. As for the benefits of HPV vaccines, VARRC assumed that the HPV vaccine would prevent 13,000-20,000 people of future incidence of CC among those already vaccinated (29). Even though the scientific investigation of the vaccine's safety was conducted by VARRC and no relationship between the severe adverse effects and vaccination concluded, the perception of the risk of adverse events still remained among the people. The existence of the hesitancy was reflected in the low vaccination coverage (24).

4.3.2 Introduction of a new vaccine

HPV vaccine is relatively new. Although experts calculated the cost-effectiveness of this vaccine (70) before the introduction of a NIP, the impact in the long term of this vaccine cannot be guaranteed: even completely vaccinated, the vaccines cannot prevent 100% of the CC nor HPV infection, this might lead the vaccine hesitancy.

4.3.3 Mode of administration

There is little literature that mentioned about the mode of administration of HPV vaccination in Japan. As some girls, who experienced the severe pain, with the intramuscular injection during the vaccination, expressed the feelings of fear for the vaccine, healthcare providers have a responsibility to explain about the intramuscular injection before vaccination and make an effort to reduce the pain with improving injection skills (65).

4.3.4 Design of vaccination programme/Mode of delivery

The mode of delivery was identified as a barrier regarding of the process of vaccination. Wakimizu et al. (65) reported through the interviews that in all cases for the HPV vaccination, mothers searched the healthcare institutions for HPV vaccination and made an appointment, then on the day of immunisation, the mother took the girl to the institution. Although free access is accepted in Japan, the process of seeking for the institutions and making an appointment is time-consuming. In addition, there is a limitation of available hours for appointments of the institution. It is also mentioned in the busy schedule of the girls. This inconvenience of access for HPV vaccination could be one of the barriers. Another research in one rural district (58) referred by the mothers that the school vaccination was desirable regarding scheduling convenience.

4.3.5 Reliability and/or source of vaccine supply

Regarding reliability, the lack of confidence of healthcare providers was noted in some literature. Ito et al. (69) pointed out that there is a barrier that people hesitate to discuss sexual issues even with healthcare professionals, for instance, the medical students in Japan have no practical training such as discussing sexuality. Other literature (48) described the necessity of more training or knowledge review of HPV-related issues because of the lack of confidence of these issues among the paediatricians. It might lead to the absence of insufficient explanation about the screening test and HPV vaccination for women and girls.

4.3.6 Vaccination schedule

As it is mentioned in the process of vaccination, a scheduling inconvenience for both mothers and girls could be the barrier (65). Also, the HPV vaccines should be received three times within six months. This particular vaccination schedule is a hurdle to complete whole

vaccination during the supported ages (71).

4.3.7 Costs

The HPV vaccines are free for the target age because of the financial support by the government as long as the vaccines are registered as a routine vaccine. However, if an adolescent girl, who is outside of the target age range, but wants to take HPV vaccination, it costs approximately 50,000 JPY (about 500 USD) for the whole three times vaccinations. The cost of the vaccination was identified as an important factor and barrier (55,67).

4.3.8 Role of healthcare professionals

Healthcare professionals were found as important both as a barrier and promotive factors of HPV vaccines. When the cases of healthcare professionals do not recommend HPV vaccines, the explanation of the vaccine is insufficient, or the explanation of the vaccine focuses more on the risks of the vaccine, these would become a barrier. On the other hand, the recommendation or sufficient explanation of the vaccine from healthcare professionals would be promotive factors. Some literature (48,50,69) showed that the HPV vaccine acceptance depended on the recommendation from physicians, so the acknowledgement for both girls and mothers by the physicians is desirable.

4.3.9 Tailoring vaccines/vaccination to needs

HPV vaccines are financially supported only for the 12 to 16 year-old girls. Because those age girls are assumed to be virgin, and considering the effect of the vaccine, it is desirable not to start sexual activities. When speaking of necessity of the vaccines, caregivers cannot avoid explaining about sexual activities. As already mentioned in chapter 4.1.4.2, Japanese parents tend to hesitate to talk about sexual issues to children (55). This eligibility of the vaccine would lead to hesitancy especially to the caregivers.

4.4 Discussion

HPV vaccine hesitancy, in the context of Japan, was found in all three domains. Since there is no vaccination rate data of each district, the hesitancy level of HPV vaccination may be different depending on the communities. Notwithstanding that, the fear of the pain of the intramuscular injection, the fear of the adverse events after the events, which were amplified by the negative reports of media, were the common factors of hesitancy for the HPV vaccines. The information on the HPV vaccination by the experts and the government lacked or was not reported widely. Moreover, the readability and the accessibility of the information from them seemed more difficult than the information by anti-vaccine groups or negative reports. Although the statement of expert groups such as the Japan Pediatric Society, the Japan Society of Obstetrics and Gynecology and the WHO could have been broadened, it did not influence hesitancy sentiments well. The contents of media also seemed biased in a negative way. Besides, the information from anti-vaccine groups was easily spread even abroad, by using social media, for instance, YouTube and Facebook. To spread the correct and scientific information widely, expert groups should also have the choice to use social network tools actively such as promotion through Facebook and YouTube.

Meanwhile, Ito et al. (69) showed that, despite the mothers of the adolescent having a good level of knowledge on the HPV vaccination and the CC screening, to some extent the mothers still hesitated to take the CC screening. It means that only the acknowledgement does not directly lead to improving the HPV vaccination rate because other hesitancy factors may dominate. One possible barrier is thought to be a cultural hesitancy. It is already mentioned that the Japanese family and healthcare specialists have a tendency to hesitate to talk about the sexual issues, even the educational curriculum does not teach about sexual activities before the target age for the vaccination. Since the national educational curriculum, including

sexual education, is instructed by the Ministry of Education, Culture, Sports, Science and Technology (MEXT), and HPV vaccination and CC are instructed by MHLW, so a collaboration of those ministries to incorporate CC and HPV into the educational system, is important. Furthermore, the cooperation of health specialists and schools might be an opportunity to disseminate vaccination at schools.

Regardless of awareness, the geographical and time availability barriers were seen. To scale up the vaccination on implementation level, the convenient vaccine schedule and place should be taken into consideration. At the moment, since the health promotions were ordered to stop by MHLW, to establish the means of a reminder system such as acknowledgement of the HPV and CC through schools, would raise the awareness for HPV vaccination among girls and mothers.

Regarding the relevance of the analytical framework, for the analysis of this chapter, most of the findings could fit the framework "Model of determinants of vaccine hesitancy", and no additional factors were found. It seemed this model was useful when classifying and comparing the factors related to particular context. However, some domains overlapped and others were difficult to classify. For instance, the difference between the group influence (social norm) and contextual influence, was hard to distinguish. Also, this framework revealed that it was not able to show the strength of the relationship between each domain. In other words, it was not clear which factors were strongly affected by the anti-sentiment of the population. Additionally, in the Japanese contexts, not all factors were found in the literature review. Little literature was found in the following domains; influential leaders, religion, socio-economic, politics, experience with past vaccination and mode of administration.

Chapter 5 The relevance of anti-sentiment sentiments for HPV vaccine in HIC and LMIC for the situation in Japan

This chapter explores the relevance of anti-vaccine sentiments for HPV vaccine in HIC and LMIC for the situation in Japan.

5.1 Influence from the outside world on Japan

When the active recommendation for HPV vaccination was suspended, there seemed to be no direct influence from other countries. MHLW had been discussing the adverse events cases of other countries such as USA and UK, since before the HPV vaccine had been included as a routine vaccine. Then after the suspension, MHLW continued the investigation of the number of the other countries' adverse events in USA, European countries, and Asian countries, for instance, Vietnam, Philippines and India. Though the symptoms which are similar to CRPS have been reported in USA and UK, the relationship between the symptoms and HPV vaccines has never been confirmed so far. Even though the WHO announced the safety of the HPV vaccines repeatedly, MHLW has not followed the example of other countries' cases that did not suspend or withdraw the HPV vaccination (29).

5.1.1 The influence from India to Japan

In India, the government stopped the HPV vaccine national demonstration programme because of the advocacy of anti-vaccine groups in 2010 after seven girls' death was reported (72). There was confusion about the report from the Indian Parliament, that the report ignored the efficacy and safety of the vaccine, but suggested the vaccine led to the death of the girls (73). When the Japanese government decided to make HPV vaccines a routine vaccine, and when they decided to stop recommendation for the vaccines in 2013, India's case did not affect the government decisions as the case was not referred to during the discussion of the vaccination council of MHLW (29). Even though there was a little influence in the policy making from India to Japan, information and evidence of adverse events were rapidly shared over the countries among worldwide anti-vaccine groups. The advocacy groups of India referred the information from USA anti-HPV vaccine groups and pressured Indian Government to stop the trial (74). According to Nakada et al. (51), in contrast, after Cervarix® and Gardasil® were licenced in 2009 and 2011 respectively, the direction making of the government toward making a budget for financial support of the vaccine, on the premise of being a routine vaccine seemed to go well. The decision making of budgeting for HPV vaccines by MHLW, implies there was a national agreement already. In 2015, the Indian Parliamentary Standing Committee pressured on PATH (Program for Appropriate Technology in Health) for other countries to reconsider the HPV vaccination programmes supported by PATH (1).

5.1.2 The influence from other countries to Japan

There was the fear of side effects and reported that the fear was the barrier of intention to vaccine uptake in Greece (48). The case of Australia, in spite of the doubt for the benefit gaining of pharmaceutical companies of HPV vaccines by the committee, the decision of the committee about the implementation of Gardasil® to be a routine vaccine was once rejected but soon overturned after the lobbying activities by the vested interests (63). The policy change created doubt of HPV vaccines for people.

5.2 Influence from Japan for outside world

The information of the Japanese government decision of the stop of the proactive recommendation of HPV vaccination, broadened rapidly on international media and social networks as well. Especially the halt of the recommendation, was not appreciated by the scientific groups, but widely shared by the anti-vaccination groups in other countries (75). Larson et al. (45) described that some activists of anti-vaccine of Norway, Canada, USA and UK applauded the MHLW decision.

5.2.1 The influence for Colombia

The symptoms of severe adverse events, which were similar to Japanese cases, started to be reported from 2014, and the information spread immediately through social media such as Facebook and YouTube. Thanks to the Colombian government, that organised internet access and tools with a low price, many people got access to the information, most of them were anti-vaccination contents (1). Wilson et al. (1) showed that Japanese anti-vaccination groups also introduced the severe side effect case of a Colombian girl on YouTube video. However, those influences from Japan led the reduction of the HPV vaccine coverage in Colombia (from 80 percent to 20 percent). However, there was not enough influence to change the Colombian policy (1).

5.2.2 The influence for Denmark

In 2013, the adverse reactions after HPV vaccination, named postural orthostatic tachycardia syndrome (POTS) in Denmark, which symptoms were similar to CRPS of Japan. Specific diagnosis criteria were not defined in both cases and not recognised well among the physicians. Despite regulatory assurances, the anti-vaccine advocacy group called the safety of the HPV vaccines, and it led the decrease in vaccine uptake rate in Denmark (76). One report (1) revealed the media in Denmark featured Japanese adolescent girls who were affected by adverse events, after receiving the HPV vaccine of the documentary. The influence which supports anti-vaccine sentiments had the consequence of reducing the vaccine uptake coverage in Denmark. Nevertheless, the government maintained the HPV vaccine as a NIP with a proactive effort by the government. The vaccine coverage level gradually recovered since 2016 (77).

5.2.3 The influence for other countries

The research (45) showed that the news that the Japanese government suspended the recommendation, was taken up by several countries as negative news on suspension by the Japanese government. This led anti-vaccine movements in other countries and spread doubts on the safety of the HPV vaccine. In the Philippines and Kenya, the possibility of infertility due to HPV vaccines was announced through the news. One Kenyan article pointed out that the concerns about the fertility, due to HPV vaccine, were broad among Japanese because of the Japanese low fertility rate. The research also picked up the article of Kenya, that doubts that the WHO and the United States Food and Drug Administration (FDA), support the benefits of pharmaceutical companies to scale up the HPV vaccines.

5.3 Discussion

When the decision of the Indian government stopped the HPV vaccine clinical trials, the advocacy groups referred the information from the anti-vaccine group of USA. It did not influence the suspension of the proactive recommendation of HPV vaccine of Japan in 2013. On the other hand, the news of the Japanese government suspending the HPV vaccine recommendation was reported globally including LMIC in 2013. However, it also did not have a great influence to stop the other countries' HPV immunisation programme. Since more than 90 percent of the news, which MHLW suspended the recommendation was reported in English (45), the news seemed to spread mainly through English speaking countries such as the Philippines and Kenya. There was a feature which media picked up from the news of adverse reactions, after HPV vaccination, that at the beginning the anti-vaccination group vigorously shared information with the other countries' side effect case (78) and sent information through social networks such as YouTube and Facebook, and then, the media amplified the information from those groups nationwide. The cases of Colombia and Denmark seemed to be applicable. Eskola et al. (79) pointed out about the vaccine hesitancy movement has started from other vaccines, for instance, the polio vaccine hesitancy in a part of Nigeria and Pakistan. The anti-vaccine movement themselves are universal nowadays.

As Chandler et al. (76) recommended, it is necessary to reduce the fear for the side effects, that the governments show the trustworthy actions, like conducting scientific research and leading conclusions, that there is no causation of the severe adverse reactions reported and the HPV vaccination. Perlman et al. (80) also referred, to improve and increase education for key participants, this would increase the public trust and it would lead to the success of scaling up the HPV vaccines. Making an effort to create public trust by national and each local government is inevitable to handle the anti-vaccine groups' advocacy.

Chapter 6 Learn from the successful strategies to handle HPV anti-vaccine movements in a worldwide perspective

This chapter reviews the literature on successful strategies to deal with anti-vaccine movements towards implementation of HPV vaccination as a routine vaccine from a worldwide perspective.

6.1 HPV vaccine scaling up strategies in HIC

Prompt response by the government

Prompt response and clear communication by the governments after the events of critical media reports, side effects, or other rumours enabled to reduce hesitancy of anti-vaccine sentiments. In the case of UK, a girl died after a HPV vaccination, but the UK government investigated within 24 hours after the death and reported that the death was not attributed to the vaccine. This contributed not to the increase of the anti-vaccine sentiments (1,81). Meanwhile, persuading the skeptics of vaccination directly arguing against them can also backfire. Authorities need to highlight actual and correct information about the risk of communicable diseases and vaccines, not to focus on denying what skeptics say (82).

Well prepared to introduce the HPV vaccines by the government

The WHO (83) pointed out that the countries that implemented HPV vaccines passed through a long-term process of introduction, including advocacy, decision making, involving stakeholders, data analysis, the progress of regulation, funding and so on. It needs to be transparent. In Greece, the HPV vaccine implementation succeeded as the consequence of well-prepared campaigns of hotline calls, conducting public service announcements, the monitoring for the campaign and the surveys (84).

Tailor made implementation according to specific target groups

In Canada, there was a problem that the indigenous people felt difficulties to visit health care institutions because of the cultural barrier. To address this iniquitous situation, the government developed self-sampling CC screening kits; sampling by the self-scraping of the cervix tissues as an alternative means to the Pap test for CC screening (85). In the case of the USA, the Latinos appeared to be one of the groups at high risk of CC, however, the Spanish-speaking parents there, distrusted the safety of the vaccines. Culturally tailored interventions were introduced, such as using tools translation to their language and sessions in Spanish, practised out for the mothers with low English literacy levels, to improve their awareness and correct information of HPV vaccination (86,87).

Introduction of school vaccination

Various reports in the literature described that school vaccination as an effective strategy to raise the vaccination rate of HPV vaccines, for both HIC and LMIC. For instance, Australia has introduced school vaccination, and it was successful (81,88,89). To implement the school vaccination successfully, the collaboration with stakeholders of schools, healthcare professions and parents is required (89). As a way to get approval about HPV vaccines from parents, a school should collect a consent form signed by a parent of participants in advance (90).

6.2 HPV vaccine scaling up strategies in LMIC

The support by international funding

The introduction of the HPV vaccines to LMIC, needs a step of cooperation among the government, international organisations and the pharmaceutical industries (89). The Global Alliance for Vaccines and Immunization (GAVI) is an international organisation to support vaccinations, and the GAVI Alliance, the fund prioritised the support the HPV vaccines in 2009 and started the GAVI funding in 2013. For LMIC, the high cost of the HPV vaccines and delivery is one of the biggest barriers to introduce the HPV vaccination (77).

One pharmaceutical company agreed to offer to GAVI the HPV vaccine for 5 USD per dose. It was a drastic reduction because originally the cost of the HPV vaccines for required three doses was 360 USD (80,89). GAVI supported not only to discount the vaccine price, but also supported the introduction of the vaccine through a subsidy as a start-up expense at 2.4 USD per eligible girl for the vaccine (91). This also became a financial incentive for the country to introduce HPV vaccines. Kenya became the first Sub Saharan African country to receive the funding from GAVI Alliance, to execute a pilot HPV vaccine project and achieved a high uptake (80,92). These programs supported by GAVI, achieved mostly 70% or a greater coverage of HPV vaccination (91). PATH, an international NGO, partnered the ministry of health of each country of India, Peru, Uganda, and Vietnam and promoted HPV vaccination demonstration programs (91). In Uganda, 88.9% of the uptake rate was obtained through the school vaccination pilot programme, supported by PATH (80). PATH received a donation of HPV vaccines, from both GSK and Merck, and also was supported by the funding from the Bill and Melinda Gates Foundation (93). Pan American Health Organization (PAHO) also funded the HPV vaccine implementation projects, for the member countries and negotiated with the manufacturers, to reduce the price for HPV vaccine to 14 USD per dose in 2011 (89).

Public Private Partnership with the pharmaceutical companies

In addition, Merck launched the Gardasil Access Program (GAP) in 2009 and started pilot programs with NGOs, universities and other civil society organisations. Most of the programs achieved more than 70% of the uptake goal of the HPV vaccine (91). Bhutan and Rwanda were financially supported by Merck, and both took school-based programs and implemented the vaccine to NIP after the donated programs finished (89). Rwanda received three years donation from Merck, with high-level commitment such as the First Lady, a concrete health system and a community accomplished high intake vaccine rate (91). Some middle-income countries, for instance, Malaysia and Morocco also negotiated the price of the HPV vaccine with pharmaceutical companies from the original market price (88).

Implementation of school vaccination

Like HIC, the school vaccination programs in LMIC also accomplished a high HPV vaccination rate (83,88,91,92). A research in Kenya (92) called for the necessity of close cooperation among teachers and health professionals to increase the uptake rate for students, and the communication could be the means of providing correct information. Also, the series of initiatives could get over misunderstandings, distrust and stigma for the vaccines and healthcare providers. In a pilot programme practice of HPV school vaccination in Vietnam, parent meetings at the school were utilised to inform and educate on HPV vaccine for parents to improve the acceptance (89).

First Lady Effect

Some countries reported that a highly influential person such as the First Lady was the supporter for the decision making of the HPV vaccine introduction. The First Lady of Zambia, who was an obstetrician, attended the meeting discussing CC and then she started the advocacy for the introduction of the HPV vaccines. The government of Zambia applied for a donation from a pharmaceutical company and started a pilot programme in 2013 (83).

Reducing vaccine hesitancy

Historically, the discussion about doubts around several vaccines led to failures of the vaccination programs. The most remarkable case was the polio vaccine boycott in Nigeria in 2003 (47). Another example in Cameroon was the rumours that a public health officer utilises the children vaccinations to sterilise women, led to a decrease in immunisation coverage (47). In Brazil, it was the perception that the quality of the health system was poor, was related to the risk of incomplete whole HPV vaccination (94). The feature of these failures was, the underlying asymmetrical power relationship, with distrust and misunderstandings between

vaccination promoters and target groups to be vaccinated. This imbalance of power and distrust brought vaccine hesitancy (47). Some LMIC have succeeded to scale up the HPV vaccination, to work with trusted and influential leaders, such as religious and traditional leaders and head teachers of the schools, to speak with the parents, when they have a behaviour of hesitancy for the vaccine (83). In Tanzania, rumours which concerned infertility as the consequence of the HPV vaccines spread in the rural area, but the vaccine acceptance was high with 93% due to the correct information from popular media and communities such as the churches (1,95).

Others
The WHO helped to strengthen the registration process of new vaccines and worked with the national Pharmacy and Poisons Board, one of their roles in policy advice in Kenya. The direct collaboration with the WHO and the ministry of health of the country contributed to more trust in the decision making and implementation the vaccination (96).

6.3 Discussion

The big difference between LMIC and HIC, in the implementation of HPV vaccines from the findings was, how the government managed to collect the funding for programs. Several international organisations, such as GAVI and PAHO, and sometimes pharmaceutical companies directly funded some of the projects. For LMIC, it would be the main problem how to sustain a high vaccine coverage, as a NIP after the financial support from international funding has finished. Some literature (47,83,97) described that to provide financial incentives for vaccination participants would be a useful strategy for scaling up the vaccines. But taken into consideration, the sustainability of financial resources, the choice might be difficult by LMIC. The possible ways are as Shi J et al. (98) mentioned, to negotiate a reduction of the HPV vaccine price with the manufacturers in the long term, and to make an effort to keep or improve the high coverage rate by all stakeholders such as government, insurance companies, health professionals and caregivers.

As for Japan, it is difficult to acquire the funding for the vaccination program from external sources. However, the idea to ask the pharmaceutical companies to reduce the vaccine price could be applicable to the Japanese case. The cost for the vaccine at 15,000 JPY (approximately 150 USD) per dose is a heavy burden for the national finance. Besides, if one takes into consideration the follow-up case, in which for older girls beyond the target age who did not complete the full vaccination, have to pay for the expense by girls or family themselves, this would constitute a significant barrier to completion of uptake of vaccines. Another idea is to provide a financial incentive such as a reduction of a social insurance premium. Under the present healthcare system in Japan, the local governments are responsible for promoting immunisation. However, the health insurance associations should also be responsible for the prevention of the insured people. To improve the vaccine coverage, the further financial support by the government, the insurer or the producer would be necessary.

Regarding the mode of delivery, school-based vaccination achieved a high coverage compared to clinic-based vaccination both in HIC and LMIC from the findings (81,83,88,89,91,92). In the context of LIC, one study (89) pointed out that the school-based programs were not affordable by some national budgets of LIC, and there were concerns that it was not possible to reach all the target aged children because some of the girls do not go to any school due to the workload. Given the situation in Japanese low vaccine coverage, the school-based vaccination might be superior in the perspective of convenience for the girls and caregivers. Probably, it would be more expensive to execute the school programme than the clinical-based vaccination. Since almost all the target-aged girls belong to a junior high school, unless there is any special or strong reason, most of the girls will accept the vaccination because of peer pressure. But the vaccine resistance of students and parents would remain, so getting

rid of anti-sentiment for the vaccine, schools and healthcare professionals who inject vaccines, should establish a system that provides parents and children with correct information at the same time. In the case of school-based vaccination, it also has a necessity for the girls and mothers to acquire the adequate consent of HPV vaccination in advance. If it takes time to ask for a consent form from them, the easier process to carry out the vaccination is conceivable, for instance, if only a parent wants to refuse vaccination, he/she should be asked a statement to refuse (opt-out procedure). Also, mandatory immunisation is evaluated as an effective mode of raising the coverage rate in other vaccines (89). Already mentioned in chapter 4.1.5, the Japanese government once implemented mandatory immunisation but stopped due to an opposition of citizens. The vaccines for children are recognised as if obligatory as a social norm, but it seems difficult to introduce the HPV vaccine as a mandatory vaccine because the target ages and the routes of infections are different from those of vaccines for children.

In order to deal with the HPV vaccine hesitancy and distrust from the side of politics, the government should not only make an effort to maintain a transparent and public-opened system but also disclose information on the new vaccines aggressively and speedy, including utilising social media. One study (94) suggested that interventions using social media, could be effective for whom already had an interest in the vaccination or who were familiar with social media. At the same time, since social media are also easily misused to spread disinformation, it could be dangerous if it not managed well. In the case of Japan, the government stopped the vaccination recommendation without well-discussed reasons and provided little information. In contrast, the anti-vaccine groups made continuous use of social media and spread information of severe adverse reaction cases after vaccination. This combination of communication seemed to increase the HPV vaccine hesitancy. The case of the UK government who rapidly disclosed the information after the severe adverse reaction, prevented the hesitancy increase of people (1,81). Macdonald et al. (99) also stated that if the government makes decisions openly and transparently, the conspiracy sentiments about vaccine licensing is difficult to be increased. Also, it is necessary for the public to be aware of the systems about the safety of vaccines and where to get correct information (100). To build a transparent process of policy making and open information, related to the introduction of vaccines is required to the Japanese government to reduce the vaccine hesitancy.

In Japan, there should also be a more consistent communication: now, the communication has been very ambiguous: they continued the support with funding, but did not proactively recommend; then there were the court cases where people got compensation, and so on. All this offers a very confusing message to the people. Research (101) indicated, in order to counter the negative rumours and misinformation about HPV vaccination programmes, the strategy to create awareness, provide accurate information and build acceptability were effective. Meanwhile, it is difficult to convince the people who have a strong ideology of rejecting biomedical and science. Focusing on the target girls and mothers who are still curious and doubting about vaccine safety and efficacy is effective (102). Also, some articles (92,94,103,104) recommended dialogue-based interventions or education sessions to girls and parents, by health care promoters through community engagement to be most effective to build trust and improve knowledge of vaccination. Although it is hard to strengthen communication among the stakeholders at the community levels, in the current situation that the proactive vaccination recommendation stopped, it is desirable after resuming the recommendation of HPV vaccines and also desirable to apply communication toward other vaccines promotion.

Chapter 7 Conclusions and recommendations

This chapter provides conclusions on the main challenges for resuming recommendation and scaling up of HPV vaccination in Japan from previous chapters. Then, provides general recommendations that Japanese policy should adopt from lessons learned from other countries' strategies.

7.1 Conclusions

It has been more than four years since the MHLW suspended the proactive recommendation of the HPV vaccination. The low vaccination coverage without any health promotion activities by local governments will affect future prevalence and mortality from CC. Even though the awareness is high among the target girls and their mothers, the barriers to the uptake of the HPV vaccine still remain. Already MHLW concluded that the adverse effects were not related to the HPV vaccines, but because the evidence gathered was not considered enough, the suspension was not withdrawn. During these four years, the anti-vaccine groups vigorously advocated with main local media on their side and promoted using social networks. Currently, the vaccine hesitancy appears to spread to other vaccines as well as HPV vaccines. For hepatitis B vaccine, which was introduced as a routine vaccine from October 2016 onwards in Japan, the anti-vaccine movements also emerged. Furthermore, the anti-vaccine movement influences other developed countries through sharing social media information mainly by anti-vaccine groups.

On the contrary, the pro-vaccine groups represented by the medical professionals were less influential to remove the barriers. To reduce the hesitancy affected by anti-vaccine information, it is necessary for the government to make an effort to create public trust by making use of social media. Additionally, communities and health professionals also need to engage in dialogue-based communication with adolescents and mothers, in educational places to develop sexual discussion in an early age. Promoting those activities will lead to a smooth introduction and scaling up not only HPV vaccines but also for other vaccines, and maximise the effectiveness of the vaccination in Japan.

7.2 Recommendations

Based on the findings of this study, the anti-vaccine movement is very difficult to counter, and exchanges with other countries, who face similar problems, may be recommended. It needs to be realised that anti-vaccine sentiments are not just a question of a 'lack of information', it is about sentiments and fear. Recommendations below are made to reduce the anti-vaccine sentiments and resume the proactive recommendation for the HPV vaccination of Japan.

7.2.1 Managing the quality of the information

- Clarify the process and discussion of vaccine introduction, and assure the readability of the report of the HPV vaccine safety with a scientific perspective.
- Avoid any impression of conflicts of interest, and when rumours about such things appear, communicate clearly and transparently on these questions.
- Clarify the criteria for the adverse reactions and organise a reporting system.
- Improve the quality of the information collecting system of the local governments to report the number and situation of side effects, after the vaccination at the local and national level.
- Make use of the social network such as YouTube, Facebook and Twitter to disseminate health promotional information and proactively monitor the discussions to react to concerns when they appear, and threaten to undermine public trust.

7.2.2 Improving the attitudes of the citizen for HPV vaccination

- Incorporate the vaccination and sexual issues like HPV, CC, STI, family planning to the

junior high school life skills curriculum through the collaborations of the MHLW and the METI. The curriculum should also be taught by the health care specialists.
- Incorporate a practical training and education of dealing with the sexual issues and the scientific perspective of safety for healthcare professionals and medical students.
- Make use of the Parents Teacher Associations to improving their understanding of the benefits and the risks of the HPV vaccination and CC.
- Make use of the community activities and of local networks of civil society including the NGO to encourage the HPV vaccination.

7.2.3 Promotion of the effectiveness of the HPV vaccination implementation

- Develop and implement a clear and sustainable strategy and regime to achieve the introduction and scaling up the new vaccines.
- Collaborate actively with international organisations to share the useful strategies about implementation and scaling up vaccinations.
- Introduce school based vaccination with the collaboration of the local health professionals and the schools.
- Include rational/scientific information on vaccination in school curriculums, for instance in biology or other disciplines.
- Negotiate with the pharmaceutical companies to discount the price of the HPV vaccines.
- Set financial incentives for HPV vaccination and remove the financial burden for uptake.

The priorities of these recommendations are first, managing information (7.2.1), secondly improving attitude (7.2.2), and at last promotion of the effectiveness of implementation (7.2.3). Regarding the management of the quality of the information, these are recommended to take action as soon as possible, because they can be achieved without an additional budget of the government. However, the recommendations of 7.2.2 and 7.2.3 seem more difficult to execute in the short term, due to the necessity of committing other institutions/communities and they need more budget, they should be implemented to achieve scaling up of the HPV vaccination. There is a limitation of the sustainable policy and strategy for HPV vaccination since as mentioned in the chapter 1.3.3 already, the policy is affected by the leading party and the results of the elections.

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