

VACCINE CONFIDENCE

JAPAN LITERATURE
REVIEW

April 26, 2022

Ogilvy CONSULTING

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Japan | 07 | Appendix |
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towards Vaccines | | |

AGENDA

OVERVIEW

LITERATURE REVIEWED

Methodology

- We culled academic databases, Google Scholar, and Google News for articles on “Japan” OR “Japanese” and:
 - “vaccine hesitancy”
 - “HPV vaccination”
 - “vaccine attitudes”
 - + others
- Limited time scope to 2017-present

28

Academic Papers

Elsevier, MDPI, University of Helsinki, Frontiers in Public Health, The Lancet Regional Health

4

6

Articles

New York Times, BBC News, CDC, The Mainichi, Asia Pacific Foundation of Canada, The Guardian

GLOSSARY OF TERMS & ABBREVIATIONS

MHLW

Ministry of Health, Labour & Welfare

Cabinet level ministry of the Japanese government

NIP

National Immunization Plan

Outlined by the MHLW, a list of vaccines that are strongly encouraged (but not mandatory); by law, local governments are required to provide recommendations to individuals of the vaccine's target groups, called "proactive recommendations"

VARRC

Vaccine Adverse Reactions Review Committee

Part of MHLW, the body that reviews vaccine suspension or reinstatement

PVL

Preventive Vaccines Law

Passed in 1948, a law that mandates the general public must be vaccinated against infectious diseases

[x]vHPV vaccine

X indicates the number of HPV strains the vaccine is effective against

e.g., 2v = bivalent, 9v = nonavalent

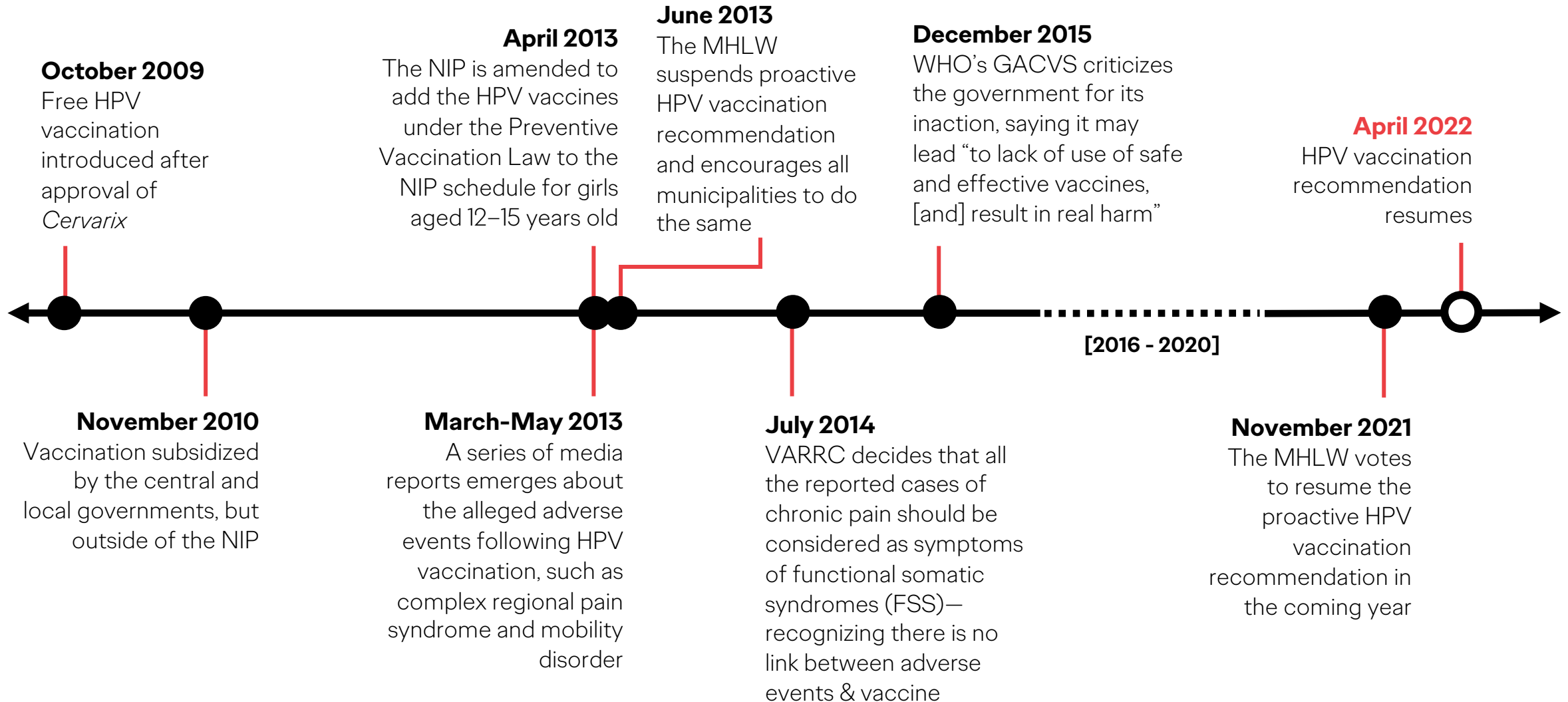
GACVS

WHO's Global Advisory Committee on Vaccine Safety

OECD

Organization for Economic Cooperation & Development

TIMELINE OF THE HPV VACCINE IN JAPAN



BEHAVIORAL SCIENCE FINDINGS ON HPV IN JAPAN

KEY BEHAVIORAL FACTORS IMPACTING VACCINE HESITANCY

Importance of Consensus—*Wa*

Traditional Japanese values place high importance on the power of consensus and the notion of harmony within a group (*wa*). As a result, many physicians and gynecologists have been waiting for the MHLW's recommendation to be reinstated in order to engage in active conversations with their patients, despite any private concerns they may hold

Cultural Collectivism—*Giri*

The COVID-19 vaccine has seen higher administration rates than the HPV vaccine, likely due to Japan's historically collectivist views and deep-rooted sense of social obligation or duty (*giri*). Many people chose to get vaccinated for the health of their community, whereas vaccinating for HPV is viewed as a choice that primarily affects one's own health

Regulatory Focus + Overestimation

Japanese mothers tend to give more weight to the potential risks posed by vaccines as opposed to the benefits. Additionally, for the HPV vaccine it was found that Japanese mothers underestimate the incidence and mortality associated with cervical cancer and overestimate the probability of severe adverse effects

Present Orientation

The benefit of the HPV vaccine is undermined by the fact that in 2013 they were only *expected* to be effective in preventing around 60% of cervical cancer cases, and it would take ten to fifteen years until anyone could see how much the incidence of cervical cancer would actually be impacted. The potential future benefit is not as clear as the current risk perceived by many mothers

STATISTICAL RESEARCH ON HPV IN JAPAN

HPV VACCINATION & CC SCREENING

90%

Of cervical cancers are caused by 9 HPV types

Types 16, 18, 6, 11, 31, 33, 45, 52 and 58, all of which are covered by the 9vHPV *Gardasil*

60%

Average vaccination rate

In OECD countries; coverage in the UK, Australia, Canada & Sweden is around 80%

0.6%

Vaccination rate in Japan

For those born in 2000 or later, down from over **70%** for those born between 1994-1999

99%

Of all cervical cancers are caused by HPV

Accounting for all 6.5% of all female cancers, and 7.7% of all female cancer deaths

84.5%

Screening rate in US

For cervical cancer (by biennial Pap smear)

30-40%

Screening rate in Japan

Lagging behind the US [left] and other OECD countries' average of 60%

THE CATCH-UP GENERATION & REINSTATEMENT

19.7%

Infection rate of high risk HPV in unvaccinated women

Vs. a 12.9% infection rate for vaccinated women

5-5.7K

More cancer deaths estimated among the catch-up gen (2013-19)

When compared to estimated deaths under 2013 vaccination rate

5.4%

Abnormal cytology rate at age 20 of females born in 2000

Vs a 3.76% abnormal cytology rate for the “vaccination generation”

1.9%

Screening rate for 20-year-olds in the ‘vaccine suspension generation’

Relative to 1.4% for the ‘vaccine generation’

20,300

Predicted cases that could have been prevented

With complete restoration of coverage in 2020

4,100

Predicted deaths that could have been prevented

With complete restoration of coverage in 2020

CURRENT JAPANESE ATTITUDES TOWARDS VACCINES

KEY FACTORS IMPACTING VACCINE ATTITUDES

Mis- and Disinformation

- The MHLW's withdrawal of the proactive recommendation inadvertently misinformed the public as to the safety of the vaccine and was perceived as an official medical denunciation (even though doctors were still able to recommend the vaccine)
- When the HPV vaccine was introduced, a 'Victims Support Group' made and distributed a DVD showing purported side effects of the vaccine, which was extensively covered on news programs without factual challenge

Lack of Transparency

- The MHLW discontinued the vaccination recommendation without a clear reason and provided little to no criteria for future re-evaluation of the subject
- In May 2013 it became public that two members of the VARRC received money from Merck and GSK, fueling rumors of a government conspiracy

Poor Communication

- During the suspension, only 97 of 1,741 municipalities sent notifications about the HPV vaccine to the target aged group of girls
- In 2017, the MHLW changed the official HPV vaccine leaflet to say *"this leaflet is intended to provide information about cervical cancer and HPV vaccines. MHLW is not sending recommendations but providing information so that those who wish can vaccinate"*

Sex Education & Norms

- Familial discussions about sexual health are extremely rare, and some Japanese patients struggle to discuss sexual issues with a healthcare provider
- Sex is still a taboo subject in government—oral contraception wasn't approved in Japan until 1999 (39 years after its development)
- Vaccine opposition groups posit that only women who engage in 'risky' sexual behavior are at risk for cervical cancer

VACCINE ATTITUDES AMONGST DOCTORS

83.3%

Of OB/GYNs believe the govt should restart the recommendation

Relative to 61% in the first wave of the survey, and 73.6% in the second

84.6%

Of OB/GYNs surveyed recommended the HPVV to teenagers

Relative to 65.2% in the first wave of the survey, and 70.1% in the second

36.7%

Of OB/GYNs chose to vaccinate their own daughters against HPV

53%

Of physicians support reinstating the proactive recommendation

However, only 21% are reported educating patients about HPV

44%

Of physicians surveyed actively recommended the vaccine

But 90% said they would with a government recommendation

51%

Of pediatricians did not feel confident discussing HPV & STIs

Relative to internists at 52% and OB/GYNs at 14%

COVID-19 VACCINE HESITANCY AND ITS ASSOCIATED FACTORS IN JAPAN

- Among 23,142 responses analyzed, the proportion of **COVID-19 vaccine hesitancy in 2021 was 11.3%**
 - Factors associated with the hesitancy were **female gender, living alone, low socioeconomic status, and presence of severe psychological distress**
 - Other possible factors related to COVID-19 vaccine hesitancy included: personal history of COVID-19 infection, fear of COVID-19-induced death, perceived likelihood of getting infected with COVID-19 themselves, **distrust toward the government, distrust toward government policy on COVID-19, the thought of embarrassment of getting infected with COVID-19 themselves**, severe psychological distress, and living in a prefecture with a high proportion of COVID-19 cases
- Recent research suggests that **people with lower socioeconomic status and severe psychological distress are more vulnerable to disinformation and misinformation** about COVID-19

JAPANESE PARENTS' ATTITUDES ON HPV

- In Japan, **mothers are the main decision maker** when it comes to their daughters' vaccination; research shows that a fathers' participation in the mothers' decision-making did not increase the likelihood of HPV vaccination for their daughters
- The third wave of a study surveying mothers of HPV unvaccinated daughters from 12-16 indicated that the **prolonged suspension of the government recommendation has increased vaccine hesitancy**, and that the recommendation was a significant factor in their decision making
- **Mothers' vaccine confidence increased when doctors discussed the HPV vaccine with them while using an informational leaflet**

38.8%

Of target-age girls were not aware of the HPV or its significance

And 33.8% of their mothers wanted to get appropriate information and a consultation from their local government

16

38.4%

Of mothers could not decide whether to vaccinate for HPV

Stating that they did not have adequate knowledge about the virus (vs. 45% in target-age girls)

INSIGHTS & RECOMMENDATIONS

KEY RECOMMENDATIONS FROM RESEARCH

Engage with professional assns.

Much of the misinformation and confusion surrounding the suspension was due to the lack of consistent input from experts. Research recommends that going forward, health professionals should create an alliance to influence policy makers to help deliver education to health care providers and end-users.

Give victims—and advocates—a voice

While anti-HPV vaccination websites often use narratives about vaccine side effects, pro-HPV vaccination websites exclusively use statistical information. Given the persuasive force of narratives in the recognition of risks, many experts suggest for vaccination promoters to utilize positive vaccine and survivor narratives in communications, such as profiling a cervical cancer survivor or someone who was previously concerned about the HPV vaccine.

Overcommunicate

A communication plan needs to involve guidance not just for face-to-face communication between patient and physician, but also for messaging to a broader public. Experts recommend using every opportunity possible to provide information that promotes more comprehensive, science-based views, including increasing the level of communications deployed by local, state, and federal governments, improving overall sex education programs, and creating a plan to positively influence media coverage

Meet patients where they are

Rather than having mothers actively seek out information from their local government, experts recommend a multi-channel strategy tailored to both mothers and daughters (especially because teenagers are the least likely age group in Japan to consult a doctor). This includes activating traditional methods like a telephone hotline, an FAQ guide, and TV and radio messaging, but also less traditional methods like being active on social media and proactively monitoring for vaccine sentiment

TAKEAWAYS & OUTSTANDING QUESTIONS

BEHAVIORAL FACTORS

Importance of Consensus –
Wa

Cultural Collectivism – Giri

Regulatory Focus +
Overestimation

Present Orientation

VACCINE HESITANCY FACTORS

Mis- and Disinformation

Lack of Transparency

Poor Communication

Sex Education & Norms

SUGGESTIONS FROM RESEARCH

Engage with professional
associations

Give victims & and
advocates a voice

Overcommunicate

Meet patients where they
are

OUTSTANDING QUESTIONS

How might the current debate in Japan about changing gender roles and female autonomy influence the propensity to support HPV vaccination?

Has there been a significant change in vaccine attitudes now that the proactive recommendation has been reinstated?

While mothers are the main decision makers (and the target of research), what kind of consideration do they give to their daughters' preference when it comes to vaccination?

What, if any, public visibility do the issues of the catch-up generation have? How well known to the general public are the potential challenges they face?



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APPENDIX

ACADEMIC STUDIES REVIEWED

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- Risa Kudo , Masayuki Sekine, Manako Yamaguchi, Megumi Hara, Sharon J. B. Hanley, Yutaka Ueda , Asami Yagi, Sosuke Adachi, Megumi Kurosawa, Etsuko Miyagi, and Takayuki Enomoto. Vaccines. MDPI 2021. *“Internet Survey of Awareness and Behavior Related to HPV Vaccination in Japan” HPV Vaccines.*
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- Yutaka Ueda, Kayoko Katayama, Asami Yagi, and Tadashi Kimura. Cancer Prevention Research. AACR 2021. *“The Chasm We Must Cross in Japan for Re-promotion of the HPV Vaccine” HPV Vaccines.*
- Mugen Ujiie, Taito Kitano & Shinya Tsuzuki. Human Vaccines & Immunotherapeutics. Taylor & Francis 2021. *“Changing trends in HPV vaccination in Japan” HPV Vaccines.*
- Masayuki Sekine, Risa Kudo, Manako Yamaguchi, Sharon J. B. Hanley, Megumi Hara, Sosuke Adachi, Yutaka Ueda, Etsuko Miyagi, Sayaka Ikeda, Asami Yagi and Takayuki Enomoto. Vaccines. MDPI 2021. *“Japan’s Ongoing Crisis on HPV Vaccination” HPV Vaccines.*

ACADEMIC STUDIES REVIEWED

- Mostafa Saidur Rahim Khan *, Somtip Watanapongvanich and Yoshihiko Kadoya. *“COVID-19 Vaccine Hesitancy among the Younger Generation in Japan” Covid-19 Vaccines.*
- Ryo Okubo 1,* Takashi Yoshioka 2, Satoko Ohfuji 3 , Takahiro Matsuo 4 and Takahiro Tabuchi. *“COVID-19 Vaccine Hesitancy and Its Associated Factors in Japan” Covid-19 Vaccines.*
- Kate T Simms*, Sharon J B Hanley*, Megan A Smith*, Adam Keane, Karen Canfell. *“Impact of HPV vaccine hesitancy on cervical cancer in Japan: a modelling study” HPV Vaccines.*
- Heidi J Larson. *“Japan’s HPV vaccine crisis: act now to avert cervical cancer cases and deaths” HPV Vaccines.*
- Alexandre de Figueiredo*, Clarissa Simas*, Emilie Karafillakis, Pauline Paterson, Heidi J Larson. *“Mapping global trends in vaccine confidence and investigating barriers to vaccine uptake: a large-scale retrospective temporal modelling study” HPV Vaccines.*
- Ly Nguyen, Candice Ruck. *“Japan’s Vaccine Hesitancy Has Implications for COVID Control, and the Summer Olympics” Covid-19 Vaccines.*
- Tsuyoshi Okuhara*, Hirono Ishikawa, Masafumi Okada, Mio Kato and Takahiro Kiuchi. *“Persuasiveness of statistics and Patients’ and Mothers’ narratives in human Papillomavirus Vaccine recommendation Messages: a randomized controlled study in Japan” HPV Vaccines*

ACADEMIC STUDIES REVIEWED

- Shuhei Nomura, PhD, Akifumi Eguchi, PhD, Daisuke Yoneoka, PhD, Takayuki Kawashima, PhD, Yuta Tanoue, PhD, Michio Murakami, PhD, Haruka Sakamoto, PhD, Keiko Maruyama-Sakurai, MPH, Stuart Gilmour, PhD, Shoi Shi, PhD, Hiroyuki Kunishima, PhD, Satoshi Kaneko, PhD, Megumi Adachi, BN, Koki Shimada, PhD, Yoshiko Yamamoto, PhD, Hiroaki Miyata, PhD. *“Reasons for being unsure or unwilling regarding intention to take COVID-19 vaccine among Japanese people: A large cross-sectional national survey” Covid-19 Vaccines.*
- Yutaka Ueda^{1*}, Asami Yagi¹, Hazuki Abe¹, Satoshi nakagawa¹, Ryoko Minekawa², Haruo Kuroki³, Ayako Miwa⁴ & tadashi Kimura¹. *“The last strategy for re-dissemination of HPV vaccination in Japan while still under the suspension of the governmental recommendation” HPV Vaccines.*
- Asami Yagi¹, Yutaka Ueda^{1,*}, Mamoru Kakuda¹, Satoshi Nakagawa¹, Kosuke Hiramatsu¹, Ai Miyoshi¹, Eiji Kobayashi¹, Toshihiro Kimura¹, Megumi Kurosawa², Manako Yamaguchi², Sosuke Adachi², Risa Kudo², Masayuki Sekine², Yukio Suzuki³, Akiko Sukegawa³, Sayaka Ikeda⁴, Etsuko Miyagi³, Takayuki Enomoto² and Tadashi Kimura¹. *Cervical Cancer Protection in Japan: Where Are We? HPV Vaccines.*
- Yoshikazu Nagase, Yutaka Ueda, Hazuki Abe, Asami Yagi, Masaaki Sawada, Satoshi Nakagawa, Kosuke Hiramatsu, Tomomi Egawa-Takata, Shinya Matsuzaki, Eiji Kobayashi, Toshihiro Kimura & Tadashi Kimura. *“Changing attitudes in Japan toward HPV vaccination: a 5-year follow-up survey of obstetricians and gynecologists regarding their current opinions about the HPV vaccine” HPV Vaccines.*
- Mio Tamakoshi. *“ENACTING SCIENTIFIC KNOWLEDGE -- A Case Study of the Japanese HPV Vaccine Crisis” HPV Vaccines.*
- Diviya Santhanes¹, Che Pui Yong¹, Yan Ye Yap¹, Pui San Saw¹, Nathorn Chaiyakunapruk^{1,2,3,4} & Tahir Mehmood Khan. *“Factors influencing intention to obtain the HPV vaccine in South East Asian and Western Pacific regions: A systematic review and meta-analysis” HPV Vaccines.*

ACADEMIC STUDIES REVIEWED

- Alex Vorsters !, Pierre Van Damme. *“HPV immunization programs: Ensuring their sustainability and resilience” HPV Vaccines.*
- Hirokuni Beppu, Masumi Minaguchi, Kiyoshi Uchide, Kunihiro Kumamoto, Masato Sekiguchi, Yukari Yaju. *“Lessons learnt in Japan from adverse reactions to the HPV vaccine: a medical ethics perspective” HPV Vaccines.*
- Kaori Takahashi. *“Main challenges for scaling up HPV vaccination in Japan” HPV Vaccines.*
- Alex Vorsters et. al. *“Risk factors for HPV infection and high-grade cervical disease in sexually active Japanese women” HPV Vaccines.*
- Manako Yamaguchi¹, Masayuki Sekine^{1*}, Sharon J. B. Hanley², Risa Kudo¹, Megumi Hara³, Sosuke Adachi¹, Yutaka Ueda⁴, Etsuko Miyagi⁵ & Takayuki Enomoto¹. *“Factors influencing intention to obtain the HPV vaccine in South East Asian and Western Pacific regions: A systematic review and meta-analysis” HPV Vaccines.*
- Asami Yagi,^a Yutaka Ueda,^{a,*} Sayaka Ikeda,^b Etsuko Miyagi,^c Masayuki Sekine,^d Takayuki Enomoto,^d and Tadashi Kimura,^a. *“The looming health hazard: A wave of HPV-related cancers in Japan is becoming a reality due to the continued suspension of the governmental recommendation of HPV vaccine” HPV Vaccines.*

ADDITIONAL MEDIA SOURCES CITED

HPVV: The newsletter on HPV

- Nagayasu Egawa, MD, PHD. *“HPV Vaccination in Japan” A Researcher’s View*”
- Sharon J.B. Hanley, PHD, Kate T Simms, PHD, Megan A. Smith, PHD. *“HPV vaccination: The price of inaction”*
- Sharon Hanley, Ma(hons), PHD, *“Who or what are the greatest enemies of the Japanese HPV vaccination programme?”*

ADDITIONAL MEDIA SOURCES CITED

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- BBC News, [*"Japan: From vaccine hesitancy to vaccine success"*](#)
- CDC, [*"Dr. Sharon Humiston Describes How She Recommends HPV Vaccine"*](#)
- The Mainichi, [*"Japan eyes promotion of HPV vaccines as early as FY 2022 while damages lawsuits go on"*](#)
- Asia Pacific Foundation of Canada, [*"Japan's Vaccine Hesitancy Has Implications for COVID Control, and the Summer Olympics"*](#)
- The Guardian, [*"'I was anxious at first': how Covid helped vaccine-sceptic Japan overcome its hesitancy"*](#)

BEHAVIORAL SCIENCE FINDINGS ON HPV IN JAPAN

DETERMINANT OF VACCINE HESITANCY VARY ACROSS TIME, PLACE, AND VACCINES

- A variety of factors are associated with vaccine uptake and vary in their relative strength of influence:
 - **Socio-economic status**, with both high and low income able to act as barrier or promoter of vaccination
 - **Level of education**, similarly, both higher and lower education can serve as barrier or promoter
 - **Media coverage**, with the content of the story determining whether it is a barrier or a promoter
 - **Costs of vaccine/being vaccinated**, generally acting as a barrier
 - **Social/peer pressure**, encouragement from others, or the feeling that immunization is a social norm acted as a promoter
 - **Beliefs, attitude and motivation** around health issues, with **greater health knowledge** acting as promoter
 - **Knowledge/awareness of the need of vaccines**, especially awareness of a vaccine-preventable disease acted as a promoter
- Determinants of HPV vaccine confidence **differ from other vaccines** and need to be addressed
- Determinants of HPV vaccine confidence **differ between cultures** – for example, the fear around promiscuity was not prominent in Australia

REPORTING BIAS IN ADVERSE EVENTS RELATED TO THE VACCINE

- Reports of adverse events (AE) following administration of the HPV vaccine in Japan **do not factor in the time period between the vaccination and AE** — many AEs reported up to 2018 may have occurred more than 2–5 months postvaccine
- Despite large increases in vaccine administration over time, the **incidence of reported adverse events per vaccine dose did not increase since 2016**
 - In 2016, only about 0.3% of the target population received the HPV vaccine
 - Only 878 doses were administered over December 2016–April 2017, while 35,396 doses were administered over January–March 2021
- This may be because of **reporting bias in the early period**, given that negative information about the HPV vaccine was predominant in Japan until a few years after the governmental withdrawal of the recommendation for the HPV vaccine

STATISTICAL RESEARCH ON HPV IN JAPAN

LACK OF VACCINATION ACROSS GENERATIONS HAS FUTURE IMPLICATIONS

- 20-year-old females' part of the 'vaccine-suspension generation' (born in 2000), had screening rates of 1.9%, which was **higher** than the 'pre-introduction generation' (1.8%) and 'vaccination generation' (1.4%)
- The abnormal cytology rate at age 20 of the females born in 2000, is 5.04% - **significantly higher** than that of the 'vaccination generation' (3.76%).
- Women of the '**vaccine-suspension generation**' **should receive 'catch-up HPV vaccinations'**, although its effectiveness is shown to be limited for females older than 20, they should be **strongly encouraged to undergo regular cervical cancer screening** and receive appropriate treatments for cervical lesions

IMPACT OF POTENTIAL CATCH-UP VACCINES

- The HPV vaccine crisis in Japan from 2013 to 2019 is predicted to result in an **additional 24,600-27,300 cases and 5,000-5,700 deaths** over the lifetime of affected cohorts, compared with sustained vaccination coverage at around 70% since 2013
- Had coverage been restored in 2020, including catch-up vaccination for missed cohorts with HPV9, could have **prevent 20,300 of these cases and 4,100 deaths**, and therefore most of the deaths due to the crisis could have been prevented
- With coverage not restored in 2020, an **additional 3,400-3,800 cases and 700-800 deaths** will occur over the lifetime of individuals who are 12 years old in 2020 alone, approximating the preventable cancers and deaths that will result from every year that coverage remains low

EDUCATION GAP FOR ELIGIBLE GIRLS

- More than half of the surveyed Japanese girls had **poor knowledge about cervical cancer screening, HPV, or HPV vaccines**
- Some **opponents** of the recommendations for HPV vaccination argue that **increased sexual activity of the girls who have received HPV vaccination** and their failure to seek cervical cancer screening care **may conversely increase the risk of cervical cancer**
- However, unvaccinated girls also tend to engage in high-risk sexual behavior, and thus it is even more **important to provide information on the effectiveness of vaccines and the usefulness of cancer screening**

HPV INFECTION RATES AND VACCINE EFFECTIVENESS

- In a Japanese study of 1355 vaccinated women (74.6%) with bivalent HPV vaccine and 459 unvaccinated individuals (25.4%), the HPV types 16/18 infection rate among the vaccinated group was 0.2%, the infection rate among the unvaccinated group was 2.2%, which indicated that the **vaccine effectiveness (VE) was 91.9% in preventing HPV types 16/18 infection**
 - A nonavalent HPV vaccine, which will be available soon in Japan, provides direct protection against HPV 16/18/31/33/45/52/58, responsible for approximately 90% of cervical cancers in Japan (additional 8% to the effect of the bivalent vaccine)
 - Interim analysis showed that in the cervical cancer screening for individuals aged 20 and 21 years, **the infection rate of high-risk type HPV was significantly lower in vaccinated individuals at 12.9%, relative to 19.7% in unvaccinated individuals**
- Interestingly, in young Japanese women, **the self-reported memory of HPV vaccination status tends to be inaccurate**; the negative predictive value (the probability that self-reported unvaccinated individuals actually have not received the HPV vaccine) is approximately 50%
- There is no Japanese male received HPV vaccination at public expense, because the Japanese NIP has not included men. Given the increasing incidence of oropharyngeal cancer in men, **it is important to discuss the issue of HPV vaccination for men.**

IMPLICATIONS OF MEDIA COMMUNICATIONS

- While the number of newspaper articles about HPV vaccines increased from 2010 to 2016, they started to fall after 2017 indicating a falling interest in the topic and **may indicate the general public will in the near future forget HPV vaccination as a past scandal**, despite this is the first case of strong vaccine hesitancy in Japan driven by safety concerns.
- Articles prior to March 2013 were considered to have reported HPV vaccines in a positive tone as a new option for prevention of cervical cancer., consistent with previous studies that analyzed news articles about these vaccines in Western countries. However, **articles including terms related to cervical cancer prevention decreased sharply**. This decrease may have resulted in limited knowledge about HPV infection and cervical cancer, and these limitations may have become barriers to HPV vaccination after March 2013
- The results of the present study indicate the **examined newspapers frequently conveyed negative contents about HPV vaccines**, such as adverse effects, vaccine-induced damages, and lawsuit after March 2013. Conversely, over the same period, they **rarely conveyed positive contents about the vaccines**, such as on cervical cancer prevention, positive effects of the vaccines, safety statements by the WHO, and the Nagoya study results (that showed that there was no significant increase of the appearance of 24 alleged symptoms of adverse reactions to vaccination among HPV-vaccinated individuals compared with those not vaccinated). Considering the factors associated with hesitancy toward the HPV vaccines, such as in concern about the vaccines' safety, as well as limited HPV-related knowledge, this **biased newspaper coverage may have contributed to the sharp decline in the HPV vaccination rate** from 2013

REPROMOTION OF THE HPV VACCINE IN JAPAN

- The adopter categories by which a new product penetrates the market can be divided into five groups:
 - Innovators
 - Early adopters
 - Early majority
 - Late majority
 - Laggards
- The 16.0% line (sum of the percentages of the innovators and the early adopters) is an indicator of whether a new product will penetrate the market – **Vaccination coverage has recently risen** to about 10%, to cross the 16% threshold through:
 - **Peer education:** Educating community health workers on the HPV vaccine to confidently recommend vaccination to the targeted population.
 - **Peer Promotion:** That population will be expected to pass on that recommendation to their acquaintances, resulting in widening dissemination of HPV vaccine among the majority

CURRENT JAPANESE ATTITUDES TOWARD VACCINES

GLOBAL TRENDS IN VACCINE CONFIDENCE

- Japan ranked among the countries with **the lowest vaccine confidence in the world**
- Globally, the determinants most consistently associated with improved uptake were:
 - **High confidence** in vaccines (66 countries);
 - **Trusting healthcare workers** more than family, friends, or other nonmedical sources for medical and health advice (43 countries);
 - **Higher levels of science education** (35 countries);
 - **Sex**, with women more likely than men to report any child having at least one vaccine in 41 countries and men more likely than women in just one country (Chad);
 - **Age** (younger age groups associated with increased chances of uptake in 43 countries);
 - **High information seeking behavior** (18 countries).
- **Income and religion were less widely associated with uptake**; however, when a link was found between religion and uptake, it is the minority religious groups (or those refusing to provide their religious belief) who were associated with lower probability of uptake
- Countries with higher percentages of respondents strongly agreeing that vaccines are safe, important, and effective had **higher percentages of respondents reporting that they have had their children vaccinated**
- The determinants of vaccine uptake across the globe show strong consistency, with **being male or having fewer years of education associated with decreased chances of uptake**.
- **Positive information seeking behaviors and trusting healthcare workers** more than other sources such as one's social circle for medical and health advice were associated with **increased chances of uptake**.

COVID-19 VACCINE HESITANCY AND ITS ASSOCIATED FACTORS IN JAPAN

- Among 23,142 responses analyzed, the proportion of **COVID-19 vaccine hesitancy was 11.3%** (10.9–11.7%). The proportion was higher among younger respondents and female respondents, especially among younger female respondents (15.6%) compared with the lowest proportion among older male respondents (4.8%)
 - Factors associated with the hesitancy were **female gender, living alone, low socioeconomic status, and presence of severe psychological distress, especially among older respondents**
 - Other possible factors related to COVID-19 vaccine hesitancy included personal history of COVID-19 infection, fear of COVID-19-induced death, perceived likelihood of getting infected with COVID-19 themselves, **distrust toward the government, distrust toward government policy on COVID-19, the thought of embarrassment of getting infected with COVID-19 themselves**, severe psychological distress, and living in a prefecture with a high proportion of COVID-19 cases
- Recent research suggests that **people with lower socioeconomic status and severe psychological distress are more vulnerable to susceptibility to disinformation and misinformation** about COVID-19. While all people should be vaccinated, older individuals are particularly at high risk of severe infection with COVID-19, and priority should be given to this population to reduce preventable deaths. Targeted strategies to raise awareness that negative feelings about vaccines can be manipulated through disinformation campaigns, or to elicit positive feelings that vaccination contributes to the health and well-being of the community, could be useful in activating COVID-19 vaccine confidence

OVERCOMING COVID-19 VACCINE HESITANCY IN YOUNGER AUDIENCES

- Japan is regarded as one of the least vaccine confident countries in the world – but vaccine confidence varies by demographics
 - **Younger audiences** are more vaccine hesitant than older counterparts
 - **Younger women** are more vaccine hesitant than younger men
 - **Inter-age-group differences** in vaccine hesitancy were higher among **younger men** than among younger women
- However, Japan has one of the highest Covid-19 vaccination rates
 - **Women are likely to accept vaccines as a way to reduce anxiety about the future**, as global vaccination is seen as a path to restore normalcy in life
 - Some younger vaccine recipients who are assumed to have been more vaccine hesitant have attributed getting the Covid vaccine to **peer pressure and desire to return to more social events**
 - Younger generations were also reassured **by pro-vaccination comments by politicians and doctors**
- Psychographics and behavioral patterns are also determinants of vaccine hesitancy — previous studies have found that people who have feelings of **anxiety, agitation, and sadness are more likely to be vaccinated**

JAPANESE OBSTETRICIANS AND GYNECOLOGISTS OPINIONS ON HPV VACCINES

- In the third wave of this survey, 83.3% (244/293) of the obstetricians and gynecologists now have the opinion that the Japanese government should **restart its recommendation for the HPV vaccine** – this was significantly higher compared with the first (61.0%) and second wave of survey (73.6%)
- The proportion of **doctors who recommended HPV vaccines for teenagers in their daily practice** was 84.6% (248/293) which was also **significantly higher** than in the first (65.2%) and second wave of survey (70.1%)
- Our latest survey showed that 36.7% (11/30) of obstetricians and **gynecologist's daughters** that had become the national recommended age for HPV vaccination (12 to 16 years old) were **vaccinated after the suspension** of the HPV vaccination recommendation.
- The proportion of HPV vaccinations after the suspension has increased, compared to the first (0%) and second wave of survey (16.7%), and the trend has continued to increase over the course of 5 years
- This study indicated that **the attitude of obstetricians and gynecologists in Japan toward HPV vaccination has changed positively** over the past 5 years

JAPANESE PHYSICIANS' ATTITUDES ON HPV VACCINES COMPARED TO OTHER ADOLESCENT VACCINES

- 53% of eligible physicians agreed that the HPVV should be recommended, but **only 21% reported educating about HPVV.**
- 90% of respondents indicated that they would restart HPVV for adolescents if the **MHLW reinstates their proactive recommendation**
- 44% of physicians chose the **answer “recommended actively”**
- Pediatricians (51%) and internists (52%) reported being **significantly less confident educating about STIs** related to HPV than OB/GYNs (14%)
- Japanese physicians reported support for adolescent immunizations, however they were less likely to recommend or discuss HPVV compared with other adolescent vaccines, **due to lack of governmental support for HPVV**, indicating that their recommendations would improve with government endorsement of the vaccine

VACCINE ATTITUDES IN THE SOUTHEAST ASIA REGION AND WESTERN PACIFIC REGION

- Perceptions that negatively affected intention to vaccinate include – **lower knowledge level** and **less confidence in safety and efficacy** of the vaccine, perceiving the vaccine to be expensive, **low perception of contracting** HPV infection and cervical cancer, and **lack of concrete recommendations** from healthcare providers
- Having a **positive intention to vaccinate** was **significantly higher** among women **not aware** of HPV infection and HPV vaccine – may be considered counterintuitive, but affirms the multifactorial nature of the decision-making process
- The healthcare provider was cited as the **most trusted source of recommendation** –women who **received recommendations from a healthcare provider** were **more likely to undergo HPV vaccination**
- Suggest focusing on **‘belief modification’** of the public to improve vaccine uptake by targeting information on the importance and safety of vaccines to specific sections of the community

JAPANESE PARENTS ATTITUDES ON HPV VACCINATION

- 38.8% of the targeted girls **had not heard of significance and safety** of HPV vaccine at all, and that 33.8% of the mothers of the targeted girls **wanted to get appropriate information at the consultation counter** of a local government.
- 45.0% of the targeted girls and 38.4% of their mothers replied that they could not decide whether to receive the HPV vaccine because they did **not have adequate knowledge** about HPV vaccine well.
- **Lack of information on HPV vaccine** in the targeted girls and their parents has become an additional barrier because only 5.6% of all the local governments across the nation sent leaflets containing information on HPV vaccine
- In Japan, **mothers play more important roles** for decision of their daughters' vaccination.
- **Fathers' participation** in the mothers' decision-making **did not increase the likelihood of HPV vaccination** for their daughters, however, an educational leaflet was proved to be effective to enhance fathers' enrollment for decision of their daughters' vaccination.
- Effectiveness was **enhanced** when doctors explained about HPV vaccine using with **informational leaflet**

JAPANESE MOTHERS' INTENTIONS TO VACCINATE FOR HPV SINCE THE SUSPENSION

- In the third wave of a study surveying mothers of HPV unvaccinated daughters from 12-16 indicated that the **prolonged suspension of the government recommendation has increased vaccine hesitancy**, and that **the recommendation was a significant factor in their decision making**:
 - The rates mothers who replied that they would “inoculate” were significantly higher at 9 and 23 months, but by 32 months after the suspension the rate was significantly lower
 - The rates of the mothers who replied they would not inoculate were significantly lower at 9 months and 23 months, but at 76 months was significantly higher
 - The rate of the mothers who replied they would “inoculate without any specific preconditions” or would “inoculate immediately after a restart of the recommendation” was significantly lower at 23 months, and that at 76 months after the suspension was significantly higher
- The study found that intervention with a leaflet that could be used under the suspension of the governmental recommendation did not increase the mothers’ intention to inoculate their daughters. However, a leaflet that **actively encourages vaccination** may increase the intent of vaccination.
- The rates of the mothers who replied they would “**inoculate**” were **significantly higher** in the case of receiving a **recommendation by the family doctor**.

BARRIERS TO SCALING UP HPV VACCINATION AGAIN

Public Trust issues:

- In May 2013 it became public that several members of the committee who participated the introduction of the HPV vaccine received money from MSD or GSK, feeding a conspiracy theory about **collusion between the government and the pharmaceutical companies regarding vaccine introduction**
- After the adverse reactions were reported, the pharma companies and the drug regulatory agencies were asked to submit the data of the clinical trial; they responded that 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**

Cultural issues:

- 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.

Practical issues:

- 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**
- Many **parents, especially those in rural areas**, answered they would **choose small neighborhood clinics or schools to give HPV vaccination** for their children, but only medical institutions have been allowed to provide the vaccine

INSIGHTS & RECOMMENDATIONS

HISTORY OF MHLW RECOMMENDATION SUSPENSION AND FRAMING OF THE PROBLEM

- There are several controversies for the HPV vaccine on top of normal vaccine controversy: 1) it concerns sexuality and is most effective when administered before the patient becomes sexually active, 2) it involves an ambivalent agency of adolescent vaccine recipients who are neither children nor adults, and 3) the disease it prevents is fatal to only one gender
- Reasons for recommending the vaccine:
 - The Committee on Immunization proposed to routinize HPV vaccines based on the **severity of the social loss in case of cervical cancer incidence**. Adding a vaccine to the NIP means that proactive recommendations—i.e., sending individual notifications about the vaccine from local governments—is required under the law. Vaccines on the NIP are usually either for controlling highly infectious diseases in the country, or for controlling infectious disease with high mortality [...] The committee decided to add HPV vaccination to the NIP, because in the case an individual contracts cervical cancer, there will be a “social loss”—not only in the sense of the quality of life of the patient and her family, but also in the **sense for a loss for the society including health economics, as the patient would need long-term treatment and care**
- Reasons for the suspension:
 - Though the vaccines were proven to be effective preventing HPV, they were only expected to be effective in preventing 60% of cervical cancer cases, and it would be **ten to fifteen years** until anyone could see how much the incidence of cervical cancer would actually decrease because of the vaccines.
 - There are two kinds of vaccines and ways of thinking about vaccines – one is used against diseases that require herd immunity to be eradicated, and the other is to protect oneself despite what’s going on in the community; HPV tends to be thought of as the latter
 - Author posits that “the government suspended recommendations based on an etiological uncertainty instead of epidemiological calculations and has prolonged the suspension based on the **framing of HPV vaccination as an individual’s protection by choice in contrast to seeing it as a public health issue to be promoted in a national effort**”
- While anti-HPV vaccination websites often use specific narratives about vaccine side effects, pro-HPV vaccination websites exclusively use statistical information/RWD. Given the persuasive force of narratives in the recognition of risks, the author suggests vaccination promoters utilize narratives, such as those of cervical cancer survivors

GENERAL HPV VACCINATION COMMUNICATION RECOMMENDATIONS

- Information provided to those targeted for vaccination (or their parents) **should explain what the benefits are** (e.g. what does the vaccine prevent), why the vaccine is given at a young age (more robust immune response, need for fewer doses), why the HPV vaccine needs to be delivered before the start of sexual activity, why multiple doses are necessary, how effective it is, and what are the risks (e.g. the common and less frequent side effects). This may also be an opportunity to reinforce the importance of cervical cancer screening.
- If HPV vaccine delivery is school-based, teachers and administrators may participate in training and educate girls about the vaccine. They may also coordinate information with health workers and with parents and may be a trusted source of information for pupils.
- As **GPs (and other health care professionals) are still the most trusted source of medical information**, and in some countries are the sole HPV vaccine providers, they should be aware of the evidence available, and able to respond to questions and concerns. They can benefit from training on HPV, cervical cancer as well as interpersonal communication skills with girls and families.
- The way GPs and nurses approach patients can determine acceptance or refusal of the vaccine by the patients. Resistance to vaccination has been shown to be significantly lower when there is a presumptive offer of vaccines directly to patients.
- To avoid the type of situation that has occurred in Japan, it is essential to **provide the media with accurate information**, so that they are less likely to report misinformation from other sources. It is also important to have trained media spokespeople ready, including scientific experts, who can be available to address concerns or misinformation quickly
- Communication strategies to reduce vaccine hesitancy should be **tailored to younger populations of specific age groups** rather than reliance on a one-size-fits-all communication strategy

INCREASING SOCIAL TRUST TO REGAIN VACCINE CONFIDENCE IN JAPAN

- **Education to the public** – Inadequate sex education, especially in schools, contributes to insufficient knowledge about cervical cancer among girls and their parents in Japan.
- **Communication with end users** – mass media is the most immediate source of health information for Japanese adolescents and parents, repeated reports on adverse vaccine events without information about the cancer preventive effects of the HPV vaccine, put public attention on the negative aspects of vaccination
- **Teenagers are the least likely age group to consult doctors in Japan**, making it difficult for them to develop relationships of trust with healthcare providers and to obtain accurate knowledge and confidential advice about the HPV vaccine and other health issues
- Implications for messaging include:
 - Municipalities should actively distribute information **cooperating with local providers**
 - Professional associations should create an alliance **to influence policy makers and deliver education to health care providers** and end- users
 - Politicians should integrate opinions from citizens and scientists to implement an **up-to-date policy**
 - Civil society should **share individual stories from cervical cancer patients** and **positive experiences of vaccinated girls**
 - Mass media should use more **diverse sources of information** to report more comprehensive and science-based views

GUIDANCE FOR PROVIDING INFORMATION ABOUT HPV VACCINATION TO TARGET POP

Guidance for providing information about HPV vaccination to the target population:

- **Use every opportunity; don't only focus on social opportunities.** For example, messages can be printed on the back of the girls' immunization card, the Minister of Health can talk about HPV vaccine in speeches about maternal and child health.
- **Develop a frequently asked questions (FAQ) reference guide,** with all possible questions, including challenging questions. The WHO plans to provide a basic FAQ to draw from.
- **Use language and materials girls can relate to** and have fun with, e.g., colorful materials with modern designs. In countries where text messaging is common, there may be opportunities for text-based quizzes and games in collaboration with mobile phone service providers.
- **Set up a telephone hotline;** some countries have experience setting up phone hotlines so that girls, parents and other audiences can call and ask questions. This can be an effective way for people to have a real conversation with an expert about HPV vaccine.
- A **mix of channels** is important, including radio and television, school, health workers and churches.
- Pay attention to **underserved populations**, to promote equity.
- Use **Internet and social media**; Facebook or Twitter accounts devoted to adolescent health, including HPV vaccine. Dedicate a web site to HPV vaccine (or to the vaccination program in general) where any audience can access evidence-based information, materials and FAQs. Keep this information up-to-date.
- Use **gain-framed messaging**, i.e., promoting the benefits of vaccination, rather than emphasizing the consequences of not getting vaccinated. Build on positive perceptions of vaccines, which may be most effective in promoting vaccination and minimizing stigma.

IMPLEMENTING A HPV VACCINE PROGRAM

- **Provide proper and timely support to Health Care Professionals (HCP) involved in implementing the program:** inform school-doctors, school-nurses, general practitioners, pediatricians, gynecologists and pharmacists, with timely information about the disease, the vaccine, and the program in order to create acceptance for HPV vaccination among them. Encouraging the use of additional educational credits, compensation or accreditation for such training underscores the importance health authorities attach to the training.
- **Elaborate a communication plan:** A well thought out communication plan involves guidance for face-to-face communication and for tailored communication to a broader and diverse public and should include tactics such as story-telling, involving cancer survivors, family members left behind, and an appropriate use of social media to direct readers to websites with trustworthy and reader-friendly information about the HPV, vaccination, and vaccine safety
- **Talk about screening and prevention simultaneously:** monitoring signals of hesitancy (e.g., rumors, anti-vaccine messages on social media), setting up a rapid response team and speaking with one voice are crucial strategies to mitigate confusion among parents, health care professionals and vaccinees. It is advisable to focus on the positive benefit vs risk of the vaccine and avoid negative campaigning. Engaging networks of healthcare professionals and well-informed politicians and journalists by providing them tailored and accurate information can make a difference.
- **Monitoring, follow-up and adjusting the immunization program:** But other signals, such as reporting of adverse events and potential safety issues that are reported in the media and discussed on social media are equally important as an early warning system for an upcoming crisis. Conducting regular surveys (e.g., every 2 years), act as a vaccine confidence barometer and can assist in measuring (changes in) attitudes and help guiding the program.

INCREASING HEALTHCARE PROFESSIONAL ACCESSIBILITY TO JOURNALISTS

- One study interviewed journalists to explore how they select and shape news on health issues, and offered recommendations for public health professionals to work more effectively with the media; these included, **being readily accessible for journalists, cultivating specialist medical reporters, providing reliable and useful information resources**
- Increasing the number of **health professionals who have direct and unfiltered input into issues via outlets such as blogging, and Twitter** may help promote and advocate for HPV vaccination using the strengths of online social distribution and increasing accessibility for journalists online

PERSUASIVENESS OF MESSAGING ELEMENTS

- A randomized controlled study to compare message persuasiveness between different conditions in terms of statistics, narratives, and narrators in the context of HPV vaccine communication found that **statistical only messages as well as a narrative** (of a patient or a mother) **in addition to statistical messages significantly improved mothers' attitude and intention to have their daughter(s) receive the HPV vaccine** than a no message condition (control)

BARRIERS TO OVERCOME IN COMMUNICATIONS

- **Poor risk management:** The HPV vaccine recommendation was suspended by the Japanese government despite the fact that it is difficult to obtain background incidence rates on neurological and autoimmune diseases claimed by the Victims' support group to be caused by the HPV vaccine — Japan has inadequate disease registries, no HPV vaccine registry and no national screening registry
- **Poor risk communication:** Upon suspension of the proactive recommendations for the HPV vaccine, the Ministry of Health, Labor and Welfare (MHLW) told all prefectural governors not to actively recommend the vaccine and to cease all vaccine promotion. Prefectural governors also had to inform all health boards and medical professionals of this decision. However, at the same time, the vaccine remained in the NIP and health facilities were told to continue to offer full support to parents seeking the vaccine and facilitate vaccine access. The head of the special committee investigating the AEFI also stated that the decision to suspend proactive recommendations 'did not mean that the vaccine was problematic from the viewpoint of safety', but that they just wanted to implement an investigation to help reassure the public the vaccine was safe. Therefore, the decision to suspend proactive recommendations was not based on scientific evidence and caused enormous confusions for public health officials, doctors and the public
- **An unrestrained media environment and an anti-vaccine group more organized than the government:** Around the time the HPV vaccine was introduced into the NIP, the 'Victims Support group' made a DVD, sold for 500 yen (\$5), showing the purported 'side effects' of the HPV vaccine. This DVD was broadcast extensively on news programmes, despite absolutely no evidence to show the vaccine had caused the symptoms. Media rhetoric quickly became 'scientific fact' and was rarely challenged by academic organizations or health care professionals. When two journalists dared to challenge the idea that the vaccine had caused the reported symptoms, one has ended up being sued for libel.