

JAPAN: PULLING THE PLUG

Every year, about 9,400 women in Japan are diagnosed with cervical cancer and about 3,600 of them die.¹ Cervical screening is available in Japan, but participation rates languish around 30 percent, contributing to the relatively high death rate from cervical cancer.² Attitudes toward gynecological care in Japan differ from those in the US. In Japan, cervical screening usually takes place in a women's hospital setting, where women usually go only when they are pregnant or ill. Gynecologists, mostly men, do not promote Pap tests, and insurance rarely covers it.³ The Japanese Health Ministry has long recognized that it needs to do more to encourage Japanese women to get Pap tests, something that is needed even with an HPV vaccination program.

Japan licensed Cervarix and Gardasil in 2009 and 2011, respectively.⁴ By 2010, most local governments subsidized the cost of this expensive vaccine to ensure availability. In April 2013, the Japanese Ministry of Health, Labor, and Welfare added the vaccine to the recommended schedule, thus ensuring it would be available free of charge to all eligible girls.⁵ The newspaper *Japan Times* estimated that by June 2013, 8.3 million girls had received the HPV vaccine, or 70 percent of those girls born between 1994 and 1998.⁶ Despite giving the impression of a successful program initially, the Ministry abruptly suspended its proactive recommendation on June 14, 2013, less than three months after it had added the vaccine to the immunization schedule, due to "an undeniable causal relationship between persistent pain and the vaccination."⁷ This announcement

came one day after the WHO issued a press release declaring the vaccine safe.⁸

Since then, despite significant tensions around reinstatement of the recommendation, the Ministry continues to make the vaccine available in its national immunization program but does not proactively recommend it. The result has been that uptake among girls dropped from over 70 percent in 2013 to around 1 percent in 2018, destroying corporate sales projections for Japan but, perhaps more important, undermining confidence in the vaccine in other markets.⁹ Headlines like “HPV Vaccination Crisis in Japan” in the *Lancet* epitomized scientists’ and world health officials’ surprise.¹⁰

More than many other countries, Japan has previously questioned the safety and efficacy of vaccines on a national level. In 1993, Japan suspended a measles-mumps-rubella vaccine that it introduced in 1989 after observing high rates of meningitis associated with the mumps component.¹¹ After that, the government recommended that the measles-mumps-rubella vaccines be administered separately for several years. Furthermore, the government declared all childhood immunizations voluntary as of 1994.¹² Uptake is high, but it is based on the Ministry’s recommendations, not mandates.

Another national vaccine incident occurred in 2011, when the Ministry temporarily suspended Pfizer’s Prevnar vaccine against meningitis and pneumonia and Sanofi’s HiB vaccine against *Haemophilus influenzae* type b following reports of four infant deaths. The vaccines were reintroduced after evidence seemed to clear the vaccines of a causal role in the deaths.¹³ Despite reintroduction of those vaccines, Japan’s history suggests greater caution when it comes to vaccines than in many other countries.

As early as March 2010, some HPV-vaccinated girls complained to the media of complex regional pain syndrome (CRPS) after vaccination.¹⁴ In March 2013, a month before the Ministry approved the vaccine to be added to the national program, the *Asahi* newspaper reported on 50 girls suffering from CRPS and 100 unable to attend school after getting the HPV vaccine. Television also covered the HPV-vaccinated girls. Shortly after, a group of victims and their

families held a press conference to show videos of girls with seizures and balance problems.¹⁵

Why the Ministry approved the HPV vaccine amid growing injury concerns is unclear. On June 14, the day the Ministry announced the suspension of the program, the Vaccine Adverse Reactions Review Committee (VARRC), a civil society group, held a press conference, featuring girls who claimed to have been injured by the vaccine. The girls said they experienced a range of symptoms including seizures, severe headaches, and partial paralysis.¹⁶

Critics of Japan's vaccination program do not appreciate this cautious approach, however. A letter published in *Lancet* in August 2013 after the suspension of the HPV vaccination program suggested that Japan's vaccination program suffers from a "failure of governance" and argued that "reform . . . is essential."¹⁷ The authors suggest that Japan's vaccine program should more closely model the US program, stating: "Decisions should be made by an independent advisory committee, such as the Advisory Committee on Immunization Practices in the U.S.A., rather than a committee organized by government bureaucrats."¹⁸

The Ministry discovered that the adverse events reported after Gardasil and Cervarix were many times higher than other vaccines on the recommended schedule.¹⁹ The Ministry said it wanted more time to assess HPV side effects before its next recommendation. Newspapers reported that a government task force had analyzed 1,968 reported adverse events following HPV vaccination and had found 106 of them to be serious.²⁰ The Ministry intended to decide about reinstatement of its recommendation by the following December.

In October 2013, Dr. Tetsuya Miyamoto, director of the Office of Vaccination Policy at the Ministry's Health Policy Bureau, together with other Japanese medical professionals, embarked on a six-month HPV vaccine fact-finding mission. The delegation travelled to London to meet with health officials and scientists to gather more information on the vaccines. SaneVax, which had been keeping a close eye on developments, heard of this meeting from a Japanese victim support group and a journalist with *Kyodo News*, Mr. Mutsuo Fukushima. SaneVax wanted to meet with the delegation

so that it could hear the international concerns on safety and not just the government and industry perspective. SaneVax contacted Dr. Miyamoto, and he graciously agreed to meet with SaneVax's experts to listen to their concerns.²¹

SaneVax gathered an international team of doctors and scientists, including Dr. Sin Hang Lee and others.²² SaneVax's Freda Birrell also attended. While one cannot know the effect Dr. Lee and others had on Dr. Miyamoto and his team, the December deadline to reinstate the vaccine came and went without a decision, punting reinstatement to the following year.

In January 2014, the Japanese advisory committee on immunization policy released an official report, dismissing the diverse pain and motor dysfunction girls were experiencing as psychogenic and noting that the government should "provide counseling" to the affected girls for these "psychosomatic reactions."²³ This was in direct contrast to the reports from doctors and researchers who had examined the girls, who could not explain away their conditions as "psychosomatic" in nature.²⁴

Due in large part to the efforts of Japanese Senators Yamatani and Nakagawa, *Kyodo News* journalist Mr. Fukushima, and SaneVax, Japan hosted a closed International Symposium on Adverse Reactions to HPV Vaccines on February 25-26, 2014, for physicians and scientists.²⁵ Experts from Canada, the US, the UK, France, and Japan presented, including Drs. Lee, Authier, Tomljenovic, Sasaki, Shiozawa, Kiyoshi, Hama, and Fukushima.²⁶ A public hearing was held the following day, when the Ministry of Health addressed public concerns. Dr. Lee also spoke at this meeting, and the Ministry published the minutes online.²⁷

The symposium and the public hearing were forums for dialogue between scientists critical of the HPV vaccine and those supporting its reintroduction in Japan. To date, such scientific forums with proponents and critics of the vaccine together discussing it have been exceptionally rare. They explored the plausible mechanisms whereby the vaccine is causing injury, including problems with residual HPV DNA and its combination with aluminum, causing cytokine storms and tumor necrosis factor release, leading to reported injuries

and deaths.²⁸ Dr. Harumi Sakai, a Japanese researcher and organizer of the event, suggested that the adverse event rate for HPV vaccine may be 9 percent and that women who become pregnant within two years after vaccination abort or miscarry 30 percent of their babies.²⁹

Industry-friendly presentations at the Symposium emphasized what they saw as methodological flaws in the critics' research that overstated safety concerns and injuries were just psychosomatic reactions. Dr. Lee, after presenting data from an autopsy on a girl who reportedly died from the HPV vaccine, asked the audience to raise their hands if they thought that a psychosomatic reaction could cause brain inflammation. No one did.³⁰ On February 27, 2014, the day after the Symposium and the press conference, doctors from around Japan started writing the Ministry, saying that they did not accept that the girls' symptoms were psychosomatic.

A few weeks later, on March 12, Dr. Robert Pless, chairman of the Global Advisory Committee on Vaccine Safety (GACVS), issued a statement reassuring the public of the HPV vaccine's safety; he said that its "benefit-risk profile remains favorable."³¹ As we learned in Chapter 17, this statement was planned ahead of the symposium in cooperation with the Ministry for Health. Dr. Pless attempted to refute the scientific evidence presented by Dr. Lee at the February symposium. Dr. Lee later complained to the WHO as to what he considered collusion between the Japanese Ministry and GACVS, to discredit him prior to the symposium, as discussed in Chapter 17.³² The WHO never acknowledged Dr. Lee's complaint.

At the end of March 2014, the relevant Japanese Ministry committee met again to decide whether to reinstate the HPV vaccine recommendation in its national vaccine schedule. They voted no, and the deadline passed once again.

GUIDELINES FOR MANAGING SYMPTOMS

In August 2015, despite being in the middle of an international firestorm, the Japan Medical Association and the Japanese Association of Medical Sciences issued official guidelines for managing symptoms post vaccination.³³ The Japanese Health Ministry

also published a list of medical institutions where those who needed help could go to see trained staff. There was even a helpline. The guidelines were published in Japanese and not reported widely outside Japan, until *Medscape Medical News* translated the document and published it on its website.³⁴ Incredibly, there was no coverage in medical journals or in Western mainstream media. Not only was the Japanese government refusing to reinstate the vaccination program, the Medical Association was doubling down by acknowledging that reactions were medical. Contrary to the official 2014 report that determined that reactions were psychogenic,³⁵ the guidelines specifically caution against referring to a patient's symptoms as psychogenic. Instead, doctors should refer to symptoms as a "syndrome characterized by pain of unknown etiology."³⁶

According to *Medscape*, the guidelines lay out specific instructions for medical professionals to follow when people report reactions to the vaccine.³⁷ Those include obtaining medical histories, conducting a physical exam, and evaluating severity of pain in three categories: (1) pain due to inflammation; (2) neuropathic pain; and (3) psychological pain. It also recommends blood and urine tests and referrals to specialists. The guidelines stress the importance of mental and physical care of the family, as well.³⁸ The Japan Society of Obstetrics and Gynecology acknowledged the guidelines as important but hastened to add its continued support for the reinstatement of the HPV vaccine, as it considered such adverse events rare.³⁹

At a press briefing announcing the guidelines, *Medscape* reported, the president of the Japan Medical Association recommended waiting to reinstate the vaccine.⁴⁰ The president of the Japan Association of Medical Sciences went a step further and stated that there is no proof that the vaccine prevents cancer, acknowledging, however, reports that precancerous conditions had declined.⁴¹ In other words, they recommended a "wait and see" approach while taking care of those who reacted adversely. Japan stands alone in the world for now, for taking such a cautious approach. The research group that authored the HPV vaccine injury guidelines is made up of doctors and scientists from universities and medical schools all over Japan. One of the authors is Dr. Shuichi Ikeda, who had already studied approximately 200 girls

who had suffered post-HPV vaccination illnesses. He is considered an expert in diagnosing and treating their multiple symptoms.⁴²

Dr. Ikeda may be better known in Japan for his controversial public disagreement with medical journalist Dr. Riko Muranaka, a former WHO infectious disease doctor who specialized in avian flu pandemics. In March 2016, Dr. Ikeda and his team published a research paper on a mouse experiment whereby a mouse injected with the vaccine suffered brain damage. His findings were announced in a press conference and further cemented the fears of the Japanese people over the vaccine. At around this time, Dr. Muranaka began taking an interest in the HPV controversy and wrote a series of articles in support of the vaccine.⁴³

Dr. Muranaka, criticized Dr. Ikeda's mouse study in *Wedge*, a major business magazine in Japan, and made allegations of scientific misconduct in his work. Dr. Ikeda's university conducted its own investigation and cleared him of this serious charge but did ask that he clarify his findings.⁴⁴ Soon after, Dr. Ikeda sued Dr. Muranaka for defamation, based on her statements that he falsified data in his experiment. The Ministry for Health apologized publicly if Dr. Ikeda's study had caused confusion for the Japanese people and denied that the vaccine was associated with reported symptoms.⁴⁵

Dr. Muranaka's criticism of Dr. Ikeda's findings in the mouse study made its way to the *Wall Street Journal*, where she described his study as "highly misleading," a slightly lesser charge of falsifying data and scientific misconduct.⁴⁶ Dr. Muranaka was quoted in the *Financial Times* about why she made the accusations: "It is about the consequences it [the study] has for 10,000 women and their families who get cervical cancer each year in Japan and the 3,000 who die from it."⁴⁷ Dr. Ikeda's libel lawsuit against Dr. Muranaka is ongoing at the time of writing and is not expected to conclude until late 2018. Dr. Muranaka is funding her own legal fees, although according to an article on the case, she is accepting donations from a "support group."⁴⁸ In 2017, Dr. Muranaka earned the prestigious John Maddox prize in the UK for her part in fighting HPV vaccine "misinformation," and for "championing evidence in the face of hostility and threats."⁴⁹

This controversy did not stop Dr. Ikeda's work. He was quoted in the *Financial Times* saying, "I am relieved that University proved it was not fabrication or manipulation. I will do my best for the girls suffering from adverse reactions to HPV vaccine as before."⁵⁰

There was good reason that the Medical Association and the Association of Medical Sciences were cautious about reinstating the vaccine. Dr. Shuichi Ikeda and his colleagues published clinical findings in 2017 in an article titled, "Suspected Adverse Effects After Human Papillomavirus Vaccination: A Temporal Relationship Between Vaccine Administration and the Appearance of Symptoms in Japan."⁵¹ Much like Dr. Louise Brinth's study of 53 cases in Denmark, the Japanese study comprised clinical cases referred to Dr. Ikeda at the Shinshu University Hospital in Matsumoto. This groundbreaking analysis of 120 female patients goes into great detail as to diagnostic techniques and clinical evidence of harm. The study clarifies the temporal relationship between the vaccine and postvaccination symptoms. According to the study, "the vast majority of [cases] have been ascribed to chronic regional pain syndrome, orthostatic intolerance, and/or cognitive dysfunction."⁵²

INDUSTRY PUSHES BACK

Pharmaceutical industry executives would not like to see the events in Japan repeat themselves; they fear that Japan's decision not to recommend the HPV vaccine could influence other national immunization programs to reject the vaccine. Heidi Larson, a UK anthropologist and leading proponent for the HPV vaccine, coauthored an article in a scientific journal on the "global response to Japan's suspension of its HPV vaccine recommendation."⁵³ Dr. Larson heads up the newly formed "Vaccine Confidence Project" at the London School of Hygiene and Tropical Medicine, funded by the WHO and the Bill and Melinda Gates Foundation. The project's mission is to track vaccine hesitancy worldwide by "building an information surveillance system" to monitor social media for "false" information and quickly stem bad press associated with vaccines.⁵⁴

Another industry-sponsored response, coauthored by Heidi Larson, came from the US Center for Strategic and International Studies, a Washington, DC, think tank. It issued a report in April 2015, "HPV Vaccination in Japan: The Continuing Debate and Global Impacts," after having received "generous support" from Merck.⁵⁵ This was a follow-up report to one published in May, 2014, by the same authors.⁵⁶ The Center is better known for public policy studies in cyber security, foreign policy, defense policy, and climate change but has recently started working in the area of global health to advance US interests.⁵⁷

The Center's study suggests that the accounts of adverse events from Japan are "unverified" and that the girls merely "claim" to have suffered adverse events.⁵⁸ The report states that Japan's failure in "not actively promoting HPV vaccination is putting the Japanese population at long-term unnecessary risk."⁵⁹ The authors recommend that "high-level Japanese political leadership [restore] an active recommendation for HPV vaccination."⁶⁰

The report references "antivaccine" groups that gain media attention and those who have suffered adverse events as "victims," in quotation marks to question the authenticity of their claims. SaneVax is one of the "antivaccine" groups that the report references, although it fails to mention that SaneVax supported the Ministry of Health's public hearing on February 26, 2014.⁶¹ In its commentary on the girls' conditions, the report offers no other explanation for the adverse events than psychogenesis. It notes that "members of the public may perceive this label, 'psychogenic' and the term 'mass hysteria' as patronizing and dismissive of real concerns and actual physical suffering."⁶² Despite acknowledging this concern, the report sticks by its psychogenic explanation for injuries.

The report highlights India and Japan as having failed to counter negative messages about the vaccine quickly. It points to a direct correlation between immediate responses to negative media stories and public confidence. The authors showcase Japan and India as examples of what governments should not do. The authors conclude that there have been "serious spillover effects" outside Japan and that senior members of the Japanese government should step up

to find a “lasting resolution,” presumably reinstating the national recommendation to use the HPV vaccine.⁶³

Furthermore, the authors blame social media for the controversy and refer to victim groups pejoratively as “antivaccine,” which is not a term that the advocacy groups accept as accurate. The report dwells on the role of social media and how “antivaccine groups have strengthened their control of the narrative,”⁶⁴ suggesting a kind of standoff between the Japanese Ministry of Health and the advocacy groups. The authors never seriously consider the possibility that the girls’ accounts of injury are true or that such reactions are even possible. With a central theme to dismiss all reported claims of adverse events as false, the report blames bad publicity worldwide on the Japanese Ministry for failing to reintroduce its proactive HPV vaccine recommendation.

HPV VACCINE ACTIVISTS ADVANCE IN COURT

In July 2016, a victims’ group in Japan filed a class action lawsuit against the government, Merck, and GSK for injuries from HPV vaccines.⁶⁵ The group of 119 plaintiffs, which may expand, seeks damages of 15 million yen for each injured person (around \$135,000) and access to a network of medical specialists to address their chronic health issues. Japan has a vaccine injury compensation program, and some victims may have already received some compensation at the state level. One of the claims is that the vaccine program was implemented illegally. Scientists and lawyers involved in the case published an article in 2017 about the case, saying:

Today’s diagnostics and therapeutics were created by listening to patients’ voices and conducting careful examinations. It is irresponsible to dismiss a patient’s complaint as a psychogenic reaction or a general phenomenon among young women without conducting a thorough examination.⁶⁶

Just as in India, this lawsuit is pending at the time of writing.

SaneVax has attempted to analyze why Japan dropped its proactive recommendation for the HPV vaccine. It identified three meaningful factors: (1) mobilization of the families of those who suffered adverse events; (2) engagement of medical professionals to assess the adverse events in an unbiased way; and (3) the engagement of Japanese politicians to hear both sides of the HPV vaccine debate. SaneVax, Dr. Lee, and others fully understood the power of Japan's example, as did the industry. If one country could reject the vaccine despite industry pressure, surely others could, too. Japan continues to be a center of influence in the HPV vaccine debate. Both its attention to the girls' medical needs and its refusal to recommend the vaccine to its citizens means that the world will continue to monitor what happens next.
