Scientific Evaluation of the Court Evidence Submitted to the 2019 Human Papillomavirus Vaccine Libel Case and Its Decision in Japan

Jason M. Bodily1,2*, Ikuo Tsunoda1,2,3* and J. Steven Alexander4*

1 Department of Microbiology and Immunology, Louisiana State University Health Sciences Center - Shreveport, Shreveport, LA, United States, 2 Center for Molecular and Tumor Virology, Louisiana State University Health Sciences Center - Shreveport, Shreveport, LA, United States, 3 Department of Microbiology, Kindai University Faculty of Medicine, Osaka, Japan, 4 Department of Molecular and Cellular Physiology, Louisiana State University Health Sciences Center - Shreveport, Shreveport, LA, United States

Keywords: animal model, anti-vaccination, anti-vax, HANS, HPV vaccination associated neuro-immunopathic syndrome, vaccine hesitancy, viral model

INTRODUCTION

Human papillomavirus (HPV) infects the skin and other body surfaces causing warts and other benign growths (1). Although most HPV infections are eliminated by the immune system without complications, some HPV-induced growths can progress to cancer. HPV-induced cancers, including cervical cancer and oropharyngeal cancer, are responsible for over 300,000 deaths annually worldwide (2), making HPV infection a major public health problem. Several HPV vaccines have been shown to safely and effectively prevent infection by cancer-causing HPV types, thus preventing the antecedent growths that inevitably lead to cervical cancer (3, 4).

In Japan, HPV vaccines were initially introduced in 2011, and became routinely used in 2013 when the vaccination rate approached ∼70%; however, after only two and a half months, the Japanese government suspended proactive recommendation of HPV vaccination. The suspension was based on clinical reports of suspected adverse events from a few girls after HPV vaccination. Testimonials from these girls and medical doctors in Japan were repeatedly broadcasted on TV, creating public fear of the vaccine which prompted withdrawal of government support (5).

HPV VACCINE LIBEL CASE

Public anxiety over HPV vaccination was amplified by the experimental findings that were presented to the Ministry of Health, Labor and Welfare (MHLW) of the Japanese government, on March 16, 2016 by Dr. Shuichi Ikeda, principal investigator of the research team funded by MHLW who investigated potential nerve injury following HPV vaccination. In July 2016, a class-action lawsuit against the Japanese government asking for compensation for the damage purportedly caused by the HPV vaccine was filed; this lawsuit is ongoing. The “temporary” suspension of the proactive recommendation for the HPV vaccines will have been in effect for 7 years as of June, 2020. Although evidence for the safety of this vaccine has been recognized internationally (6, 7), the HPV vaccination rate in Japan remains below 1%, thus placing coming generations of young Japanese women at unnecessary risk of cervical cancer in the future. In 2017, the Global Advisory
Committee on Vaccine Safety (GACVS) reported that the mortality rate from cervical cancer in Japan increased 3.4% between 1995 and 2005 and was understood to increase by 5.9% between 2005 and 2015 (8). Recently, Simms et al. estimated that Japan's termination of HPV vaccinations will result in 5,000 deaths due to cervical cancer (9).

The summary of the MHLW presentation by Dr. Ikeda was broadcast on the evening news show, “NEWS23” on Tokyo Broadcasting System (TBS) Television network on March 16, 2016. In that news show, Dr. Ikeda, Professor and Dean of Shinshu University, Nagano, Japan, purported to show experimental evidence of brain damage in a mouse injected with an HPV vaccine (https://www.mamoreruinochi.com/wordpress/wp-content/uploads/docs/publication/hei79-1.mp4?fbclid=IwAR3F48afCKFXyrppMtWQhDQgo3T6BdQWSLZV7DuWcrI2fuH3Y1r9JPe0Q). Dr. Ikeda explained, “Deposition of abnormal antibody was observed only in the brain section of the mice injected with the HPV vaccine. The function of the hippocampus seems to be damaged. Apparently, the brain is damaged.”

This broadcast influenced public opinion and helped raise an alarm against HPV vaccination. Two weeks after the show, the HPV vaccine “victims” announced they were suing both the government and the vaccine manufacturers.

In June 2016, in response to Dr. Ikeda's team presentation and broadcast, Dr. Riko Muranaka, a noted physician, journalist, and vaccine advocate, wrote in the business magazine Wedge that Dr. Ikeda's experimental results suffered from significant scientific irregularities, and suggested that they may have been fabricated. In response, Dr. Ikeda sued Dr. Muranaka for libel, that she had damaged his reputation as a scientist. On March 26, 2019, a court in Tokyo found Dr. Muranaka guilty of libel since the Tokyo district court could not find evidence that Dr. Ikeda intentionally engaged in scientific misconduct. On October 30, 2019, the Tokyo High Court ruled against Dr. Muranaka in a retrial of the defamation case, despite support for Dr. Muranaka from Dr. Tasuku Honjo, a Nobel laureate. Since an appeal to the Supreme Court of Japan was dismissed on March 9, 2020, the above judgement became final.

However, a critical point about this court decision was that it was based solely on the impact of Dr. Muranaka's usage of the word “fabrication” to harm Dr. Ikeda’s reputation. The decision did not assess the scientific accuracy of the experimental findings. Therefore, although the result of the trial can be (and has been) seen as a victory for anti-vaccination advocates, the actual safety of the HPV vaccine was not at issue. Although the trial was reported in several prestigious journals in English including Nature and Science (10, 11), little scientific information about the evidence used in the trial has been available in English. Because of the importance of this trial in worldwide efforts to promote HPV vaccination, we summarize the scientific evidence submitted to the trial and during Dr. Ikeda's broadcast to assess its scientific merit using our professional expertise in virology, immunology, and neuroscience.

Because the scientific accuracy of Dr. Ikeda's team data was unclear, Shinshu University formed a committee to investigate the experimental findings. Dr. Ikeda's team showed images of antibody-induced damage in the hippocampus following HPV vaccination in “a mouse” (or “mice”; in the Japanese language, a singular form is commonly used instead of a plural form in most occasions). The research team claimed that they could not find such damage in mice injected with hepatitis B virus vaccine, influenza virus vaccine or phosphate-buffered saline (shown in a Japanese slide at https://www.mamoreruinochi.com/wordpress/wp-content/uploads/docs/publication/kou07.pdf and Slide 31 in English at https://www.mamoreruinochi.com/wordpress/wp-content/uploads/docs/publication/kou17.pdf). However, it turned out that the hippocampal picture was not from a vaccinated mouse (as Dr. Ikeda said in the TV broadcast) but from a brain section from an unvaccinated mouse onto which sera collected from vaccine-injected mice were applied. Even worse, although the experiment should have been conducted using multiple mice for accuracy, Dr. Ikeda's team used serum from only a single mouse. Dr. Ikeda's presentation neglected to share this important fact. Moreover, the vaccine-injected mice were not normal mice, but rather mutant mice that are known to have abnormal antibody production (12); immunologically, normal mice should have been used in the experiment since the mutant mice could develop abnormal autoantibody production even without treatment. Under the supervision of the Shinshu University committee, the same experiment was repeated by the same research group. The second experiment demonstrated no antibody deposition on hippocampal sections, which were incubated with sera from three HPV vaccine-injected mice or three control mice; negative results from both HPV vaccine and control groups were shown in the third slide at https://www.mamoreruinochi.com/wordpress/wp-content/uploads/docs/publication/hei15.pdf).

DISCUSSION

There is a consensus in the Japanese scientific community, including the Shinshu University committee and MHLW of the Japanese government, that Dr. Ikeda's research team did not prove that HPV vaccination caused damage in mouse brains. As virologists, immunologists, and neurologists, we evaluated the evidence submitted to the trial and fully agree with that consensus. The “finding” presented by Dr. Ikeda that the HPV vaccine causes hippocampal damage was not supported by subsequent work, even performed in the same University by the same group. No credible scientist can accept the possibility of the “adverse effect” of an HPV vaccine from a single mouse hippocampal image, especially when the total number of the mice used in the experiment was withheld. As of today, Dr. Ikeda's team has neither published a manuscript on the effect of HPV vaccine using valid experimental design nor disclosed the number of mice used in the experiments broadcasted on TV. Another Japanese group published a manuscript on an animal model for HPV vaccination associated neuro-immunopathic syndrome (HANS) in a journal, Scientific Reports in 2016, but the publisher retracted the article because the experimental approach did not support the conclusions of the study (13). Therefore, experimentally, there is no evidence that the HPV vaccine can induce brain damage.
In evaluating the significance of the recent trial, it is critical to separate the legal issue of libel from the scientific issue of evidence. The evidence indicates that Dr. Ikeda’s team’s work suggests nothing about the safety of the vaccine. Even if Dr. Ikeda’s research team did not fabricate the data that he presented, the data clearly did not support his claims and therefore his research team’s “findings” do not support the notion that the vaccine is in any way dangerous. We fear that the publicity of this trial will further damage the reputation of the HPV vaccine in Japan, and perhaps worldwide. We hope that careful consideration of the evidence and of the issues involved will help put to rest some of the concerns and fears of the public and thus remove some of the barriers to this important vaccine.

AUTHOR CONTRIBUTIONS

JB and IT researched the topic and prepared the text. JA supervised and edited the text and provided feedback. All authors reviewed the manuscript and agreed with the decision to submit for publication.

FUNDING

This work was supported by awards from the National Institute of General Medical Science of the NIH (5P30GM110703, IT and JB) and the National Institute of Allergy and Infectious Diseases (R01AI118904, JB). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Funding sources also include the KAKENHI from the Japan Society for the Promotion of Science [Grant-in-Aid for Scientific Research (C) (JP20K07455, IT)], and the Research Program on Emerging and Reemerging Infectious Diseases from the Japan Agency for Medical Research and Development (AMED) (20fk0108084h0802, IT).

REFERENCES

1. Bodily J, Laimins LA. Persistence of human papillomavirus infection: keys to malignant progression. Trends Microbiol. (2011) 19:33–9. doi: 10.1016/j.tim.2010.10.002
2. World Health Organization. Cervix uteri. Source Globocan 2018. In: Cancer IARo, editor. Fact Sheet From WHO on Cervical Cancer (2019). Available online at: https://gco.iarc.fr/today/data/factsheets/cancers/23-Cervix-uteri-fact-sheet.pdf
3. Costa APF, Cobucci RNO, da Silva JM, da Costa Lima PH, Giraldo PC, Gonçalves AK. Safety of human papillomavirus 9-valent vaccine: a meta-analysis of randomized trials. J Immunol Res. (2017) 2017:3736201. doi: 10.1155/2017/3736201
4. Stillo M, Carrillo Santistevete P, Lopalco PL. Safety of human papillomavirus vaccines: a review. Expert Opin Drug Saf. (2015) 14:697–712. doi: 10.15171/14740338.2015.1013532
5. Kamada M, Inui H, Kagawa T, Mineda A, Tamura T, Fujioka T, et al. What information can change the attitude of teachers toward the human papillomavirus vaccine? J Obstet Gynaecol Res. (2018) 44:778–87. doi: 10.1111/jog.13584
6. Andrews N, Stowe J, Miller E. No increased risk of Guillain-Barre syndrome after human papilloma virus vaccine: a self-controlled case-series study in England. Vaccine. (2017) 35:1729–32. doi: 10.1016/j.vaccine.2017.01.076
7. World Health Organization. Human papillomavirus vaccines: WHO position paper, May 2017. Wkly Epidemiol Rec. (2017) 92:241–68. Available online at: https://apps.who.int/iris/handle/10665/255354
8. Meeting of the Global Advisory Committee on Vaccine Safety, 7–8 June 2017. Wkly Epidemiol Rec. (2017) 92:393–402. Available online at: https://apps.who.int/iris/handle/10665/255871
9. Simms KT, Hanley SJB, Smith MA, Keane A, Canfell K. Impact of HPV vaccine hesitancy on cervical cancer in Japan: a modelling study. Lancet Public Health. (2020) 5:E223–34. doi: 10.1016/S2468-2667(20)30010-4
10. Court ruling highlights the threat of vaccine misinformation. Nature. (2019) 568:5. doi: 10.1038/d41586-019-01031-x
11. Normile D. Japanese court rules against journalist in HPV vaccine defamation case. Science. (2019). doi: 10.1126/science.aax4915
12. Sha WC, Liou HC, Tuomanen EI, Baltimore D. Targeted disruption of the p50 subunit of NF-kappa B leads to multifocal defects in immune responses. Cell. (1995) 80:321–30. doi: 10.1016/0092-8674(95)90415-8
13. Aratani S, Fujita H, Kuroiwa Y, Usui C, Yokota S, Nakamura I, et al. Retraction: murine hypothyamic destruction with vascular cell apoptosis subsequent to combined administration of human papilloma virus vaccine and pertussis toxin. Sci Rep. (2018) 8:46971. doi: 10.1038/srep46971

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2020 Bodily, Tsunoda and Alexander. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.