

Title	Even though active recommendation for HPV vaccination has restarted, Japan's rates have not recovered
Author(s)	Yagi, Asami; Ueda, Yutaka; Oka, Emiko et al.
Citation	Cancer Science. 2024, 115(7), p. 2410-2416
Version Type	VoR
URL	https://hdl.handle.net/11094/97137
rights	This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.
Note	

Osaka University Knowledge Archive : OUKA

<https://ir.library.osaka-u.ac.jp/>

Osaka University

Even though active recommendation for HPV vaccination has restarted, Japan's rates have not recovered

Asami Yagi¹  | Yutaka Ueda¹  | Emiko Oka¹ | Satoshi Nakagawa¹ | Tadashi Kimura¹ | Koichiro Shimoya²

¹Department of Obstetrics and Gynecology, Osaka University Graduate School of Medicine, Suita, Osaka, Japan

²Department of Obstetrics and Gynecology, Kawasaki Medical University, Kurashiki, Okayama, Japan

Correspondence

Yutaka Ueda, Department of Obstetrics and Gynecology, Osaka University Graduate School of Medicine, 2-2, Yamadaoka, Suita 565-0871, Osaka, Japan.

Email: zvf03563@nifty.ne.jp

Funding information

Ministry of Health Labour and Welfare (A Health and Labour Sciences Research), Grant/Award Number: 23EA1002

Abstract

Japan has a particularly critical situation surrounding its collapsed HPV vaccination program for preventing HPV-caused cervical cancers, a problem exacerbated by the lack of a national immunization database. We have determined the year-to-year HPV vaccination uptake by Japanese females and analyzed by birth fiscal year (FY) the monthly number of people receiving initial HPV vaccination. Our analysis covers the period from the start of public subsidies in 2010 to September 2023, using data provided by local governments. We calculated the cumulative number of monthly immunizations for those unimmunized as of April (the beginning of each vaccination year). The monthly number of initial HPV vaccinations was highest in August for every FY from FY 2010 to FY 2023; a second vaccination peak tended to occur in March when the vaccination year ended. The highest number of August vaccinations occurred in FY 2011, followed (in order) by 2012, 2021, 2022, 2023, and 2013. In Japan's ongoing catch-up vaccination program for young women, the monthly number of vaccinations increased in August 2022 but then slowed the following year. After FY 2021, the cumulative vaccination coverage of subjects unvaccinated at the beginning of the vaccination year but subsequently covered by routine immunizations was slightly improved. FY 2021 was when the governmental recommendations for HPV vaccination were resumed. More recent vaccination rates are considerably lower than those in FY 2011–2012 when vaccinations were first fully endorsed. Paralyzing HPV vaccination hesitancy, which began in FY 2013, will linger in Japan in FY 2024.

KEYWORDS

cervical cancer, HPV vaccine, Japan, suspension of recommendation, vaccination rate

1 | INTRODUCTION

Globally in 2020, there were an estimated 600,000 cases of cervical cancer and 340,000 deaths.¹ Cervical cancers result mainly

from a sexually transmitted infection with a high-risk strain of the HPV, of which there are approximately 15 types. The modern nine-valent HPV vaccine is protective from at least seven of the types.

Abbreviations: FY, fiscal year; HPV, human papillomavirus; SAGE, The Strategic Advisory Group of Experts on Immunization; WHO, World Health Organization.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2024 The Authors. *Cancer Science* published by John Wiley & Sons Australia, Ltd on behalf of Japanese Cancer Association.

HPV causes cancer by integrating its genome into the nuclear DNA of infected cells, where it can lie dormant for years. The primary means of prevention of deadly cervical cancer is early HPV vaccination to prevent any HPV infection. The recommended age in Japan is between the ages of 12 and 16. Secondary prevention of cervical cancer is accomplished by regular, appropriately timed cervical screening for pre-cancerous lesions among targeted age groups. Hall proposed that appropriate HPV vaccination and cervical screening could all but eliminate cervical cancer.² In 2020, the WHO launched a global strategy for cervical cancer elimination to do just that, with a goal for all countries to achieve an HPV vaccination coverage of 90% by 2030.³ However, some countries, including Japan, are currently struggling to promote HPV vaccination.

SAGE is WHO's advisory body on vaccines and immunization. In a SAGE report on general vaccine hesitancy, they discussed the failed acceptances of the measles vaccine in parts of Europe, the polio vaccine in Nigeria and Pakistan, and the HPV vaccine in Japan as representative examples of unacceptable specific vaccine hesitancy occurring worldwide.⁴ SAGE stated, "Individual and community hesitancy and resistance to immunization must be better understood and addressed to achieve and maintain the high immunization coverage necessary for population immunity."

Japan's recent 10-year hesitancy toward the HPV vaccine is at odds with its recent open and rapid acceptance of the COVID-19 vaccines, which achieved one of the highest levels among developed countries.⁵ Japan can achieve high vaccination coverage—in a short period—through close and trusted collaborations among medical, administrative, educational, and governmental institutions via properly constructed and delivered publicity.

The status of HPV vaccine hesitancy in Japan is seemingly intractable and there is a different level of stubborn resistance to change. Japan is the only nation to have ever suspended its recommendations for what was once a national program for routine HPV vaccination,⁶ occurring even while the age-adjusted incidence of HPV-caused cervical cancer in Japan was increasing over the last 20 years.^{7,8} Among developed countries, Japan has perhaps the most urgent need to take drastic measures if it is ever to achieve WHO's cervical cancer goals.

Historically, Japan's national immunization program started in FY 2010, relatively late compared with other advanced countries, but it was quickly a great success, achieving a 70% coverage rate by early 2013.⁹ However, there were soon multiple exaggerated media reports of potentially serious adverse side effects from the HPV vaccine. In response, in June 2013, Japan's Ministry of Health, Labor, and Welfare (MHLW) announced a 'temporary suspension' of its official governmental recommendation for the HPV vaccine. Because of indecision, that 'temporary suspension' would drag on for almost 9 years, hampering Japan's efforts to curb its rising tide of cervical cancers.

It was not until FY 2020 and 2021 that a handful of local governments in Japan began again providing individualized information promoting HPV vaccination for school girls who were becoming age-eligible for routine government-subsidized HPV vaccinations. Finally,

in April 2022, the MHLW restarted its full active recommendation for HPV vaccination and simultaneously started a new program for 'catch-up vaccinations' for older girls who had foregone their previous age-eligible vaccination opportunities. This program targets the so-called 'vaccine-suspension generation' and will be time-limited, lasting only 3 years, from FY 2022 to FY 2024. This novel 'catch-up' program targets females born between FY 1997 and FY 2007 who are/will be between 17 and 27.

One of the problems with Japan's national vaccine program is that the MHLW reports the number of vaccinations by age, not by birth FY, for each vaccination fiscal year more than 1 year later than the end of the FY, making it impossible to evaluate vaccination status promptly. We aimed in this new study to determine the year-to-year coverage of HPV vaccination uptake in Japan in a more timely fashion.

2 | MATERIALS AND METHODS

2.1 | Study setting

In previous studies, we integrated and analyzed multiple published data and recalculated the HPV vaccine initial vaccination rates for each birth FY.^{9,10} The vaccination data used for the calculations of our previous reports were as follows: Japan's MHLW Science Council's Vaccination and Vaccine Subcommittee Side-Reaction Study Group, the implementation report of the emergency promotion project for HPV vaccination from FY 2010 to FY 2012,¹¹ data from the "Report on Regional Public Health Services and Health Promotion Services" published by MHLW from FY 2013 to FY 2021,¹² and the population census from FY 2020.¹³

In July 2023, the MHLW reported the results of a survey of all municipalities on the HPV vaccine implementation rates from April 2022 to March 2023.¹⁴ Data on immunization coverage by year of birth was not published, only the implementation rate, which was calculated by dividing the number of immunizers in the five grades combined by the population of one grade, not the annual vaccination rate. The implementation rate was 42%, equivalent to 8% per grade, which was significantly low. In response to these data, we considered it justified to clarify the current status of HPV vaccination in Japan by monitoring the monthly vaccination coverage in the local governments from the year when public subsidies were started in Japan. As the SAGE report pointed out, analysis and dissemination of more localized data to "better understand and address individual and community hesitancy and resistance to vaccination" is one of the necessary steps to resolve the current HPV vaccine crisis in Japan.⁴

2.2 | Study design

Because a national database system on immunization has not yet been established in Japan, obtaining data from the local municipality was the

only timely way to evaluate vaccination coverage. Two cities in Japan (with a combined total population of 1,180,000) provided the number of monthly HPV vaccine initial vaccination subjects by birth FY from the start of public subsidies in 2010 to September 2023. Okayama City is an ordinance-designated city, and Kurashiki City, which is adjacent to Okayama City, is a core city. In Japan, ordinance-designated cities have a population of 500,000 or more to which a part of the prefectural government's administrative authority is assigned. Core cities have a population of 200,000 or more, and are assigned the next largest range of prefectural administrative authority. The vaccination FY and target birth FY for each vaccination FY for which we had data are as follows: Routine vaccinations: in FY 2010, born FY 1994–1996; in FY 2011, born FY 1995–1998; in FY 2012, born FY 1996–1999; in FY 2013, born FY 1997–2001; in FY 2014, born FY 1998–2002; in FY 2015, born FY 1999–2003; in FY 2016, born FY 2000–2004; in FY 2017, born FY 2001–2005; in FY 2018, born FY 2002–2006; in FY 2019, born FY 2003–2007; in FY 2020, born FY 2004–2008; in FY 2021, born FY 2005–2009; in FY 2022, born FY 2006–2010; in FY 2023, born FY 2007–2011. Catch-up vaccinations: in FY 2022, born in FY 1997–2005; in FY 2023, born in FY 1997–2006. However, FY 2023 only provides the number of inoculations for each month from April to September.

Data were summarized for each publicly subsidized/routine vaccination and catch-up vaccination. We also examined the cumulative monthly immunization coverage of those who had not been immunized as of April, which was the beginning month of each immunization year. In the analysis of catch-up vaccination, because there was a large gap in vaccination rates between the vaccinated generation

(females born in FY 1997–1999) and the vaccine-suspension generation (females born in FY 2000–2006) at the period of routine vaccination, the data were divided according to birth FY.

3 | RESULTS

3.1 | Monthly number of initial vaccinations by routine HPV vaccination from FY 2010 to FY 2023

Figure 1 shows the monthly number of initial vaccinations by routine HPV vaccination from FY 2010 to FY 2023. It was apparent that the number of vaccinations was higher in August for all vaccination FY, and that the number of vaccinations also tended to rise in March, when the vaccination FY ends. The number of vaccinations in August was higher in FY 2011, 2012, 2021, 2022, 2023, and 2013, in that order. Only in FY 2011 and FY 2012 was the number of vaccinations above 1000. Following the resumption of the recommendation, the number of vaccinations per month has not again reached 1000.

3.2 | Cumulative HPV vaccine initial vaccination rate by routine vaccination among unvaccinated subjects at the beginning of each vaccination from FY 2010 to FY 2023

Figure 2 shows the cumulative vaccination coverage of unvaccinated subjects at the beginning of the vaccination year. For

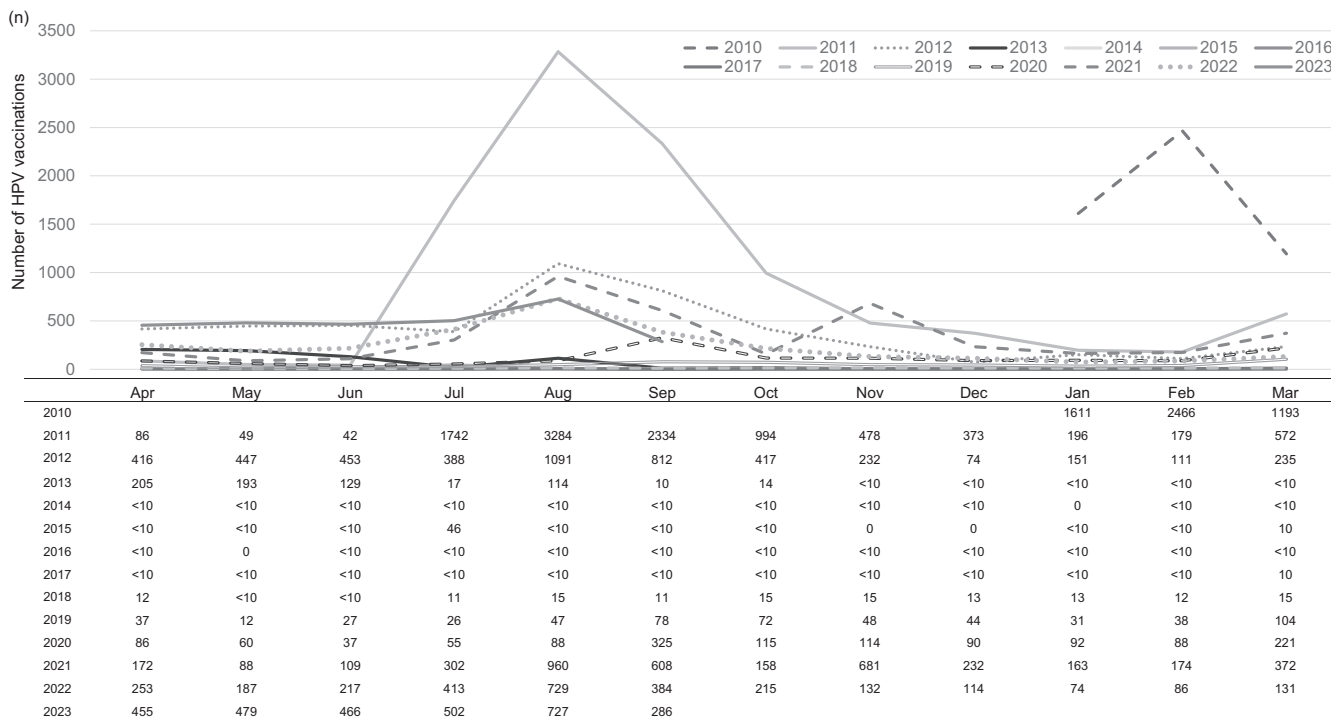


FIGURE 1 Monthly number of initial vaccinations by routine HPV vaccinations from FY 2010 to FY 2023.

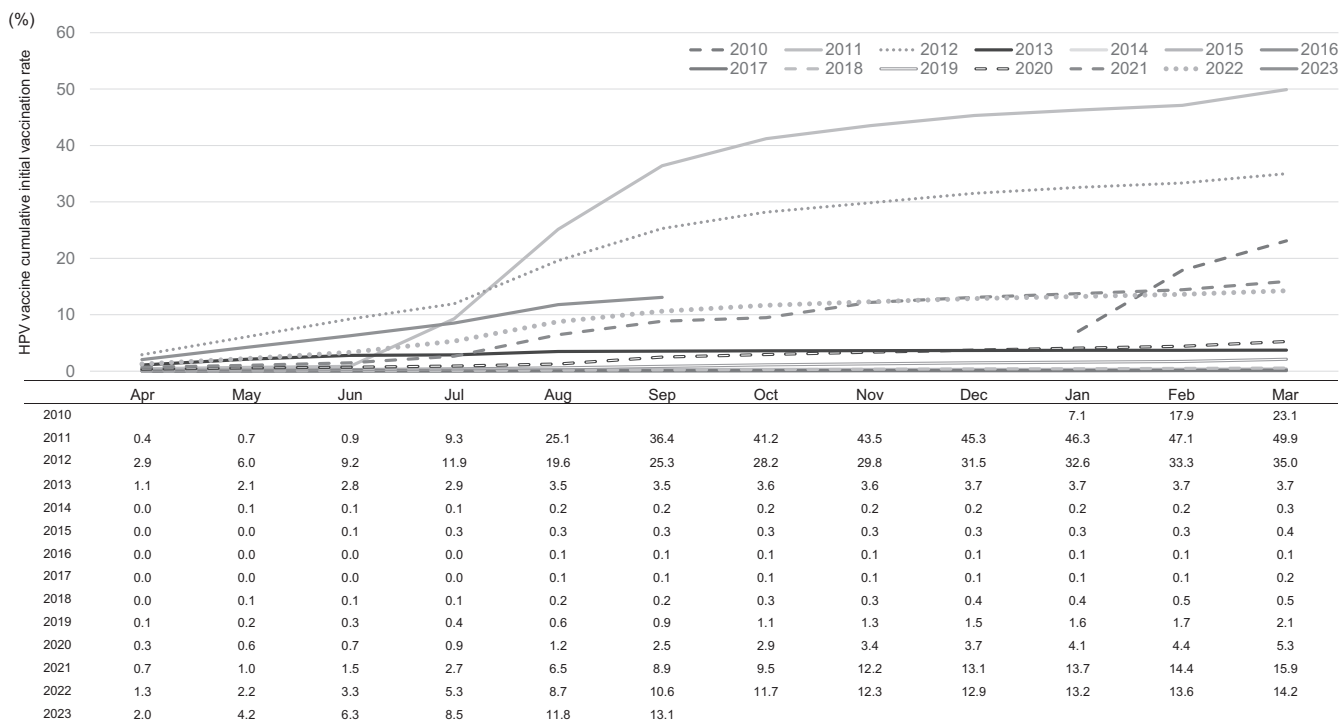


FIGURE 2 Cumulative HPV vaccine initial vaccination rate by routine vaccination among unvaccinated subjects at the beginning of each vaccination from FY 2010 to FY 2023.

routine immunizations, it was clear that the percentage stayed below 5% during the years of suspension of recommendations. The percentage slightly improved after FY 2021, when the recommendations were resumed, but remained considerably lower than those in FY 2011-2012, before the suspension of the governmental recommendation.

3.3 | Monthly number of initial HPV vaccinations by catch-up vaccination in FY 2022-2023 by generation

Figure 3 shows the monthly number of initial HPV vaccinations by catch-up vaccination in FY 2022-2023 by generation. In the catch-up vaccination, as with the routine vaccination, the number of vaccinations increased in August 2022, but growth slowed in the following FY.

3.4 | Cumulative HPV vaccine initial vaccination rate by catch-up vaccination among unvaccinated subjects at the beginning of each vaccination from FY 2022 to FY 2023 by generation

Catch-up vaccination remained low in FY 2021 and FY 2022 for both the vaccinated and vaccine-suspension generations and declined further the following FY 2023 (Figure 4).

4 | DISCUSSION

We found that the paralyzing HPV vaccination hesitancy that began in Japan in FY 2013 still lingered on in FY 2023. For routine immunizations, it was clear that the cumulative vaccination coverage of unvaccinated subjects at the beginning of the vaccination year stayed very low during the years of suspension of recommendations. The percentage slightly improved after FY 2021, when the recommendations were resumed. In each vaccination FY, the monthly number of vaccinations tended to increase in August, the summer vacation period, and in March, the last month of the fiscal year, so strengthening promotion at schools and information for targets and their parents focusing on these months, is considered effective in further improving the vaccination coverage.

As for the catch-up vaccination, it is thought that, among the vaccinated generation (females born in FY 1997-1999), the targets with high interest in the vaccine received vaccination in FY 2022, the first year of the start of catch-up vaccination, thus leaving those with low interest in the vaccine. These phenomena resulted in a low cumulative vaccination rate among the unvaccinated at the beginning in FY 2023. It is necessary to increase the number of people who are willing to be vaccinated by providing information to the non-interested group. For the vaccine-suspension generation (females born in FY 2000-2006), the cumulative vaccination rates among unvaccinated subjects at the beginning of the vaccination year improved slightly from FY 2022 to FY 2023. In order to further improve the rates, it was considered necessary to simplify the procedures for receiving

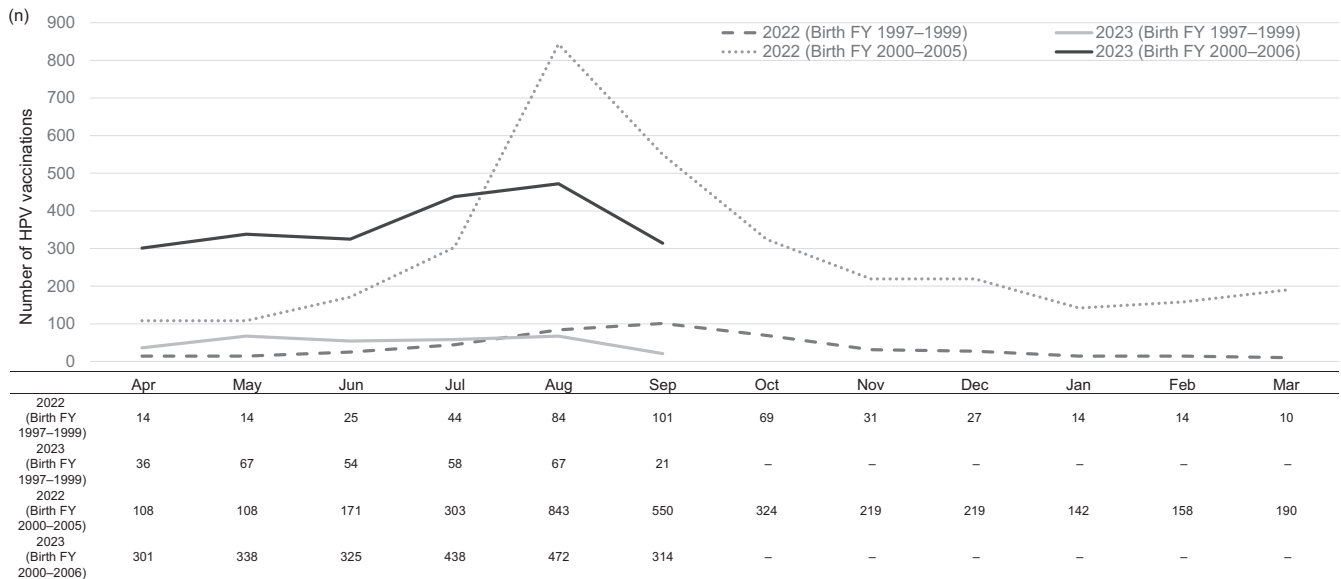


FIGURE 3 Monthly number of initial HPV vaccinations by catch-up vaccination in FY 2022-2023 is determined by generation.

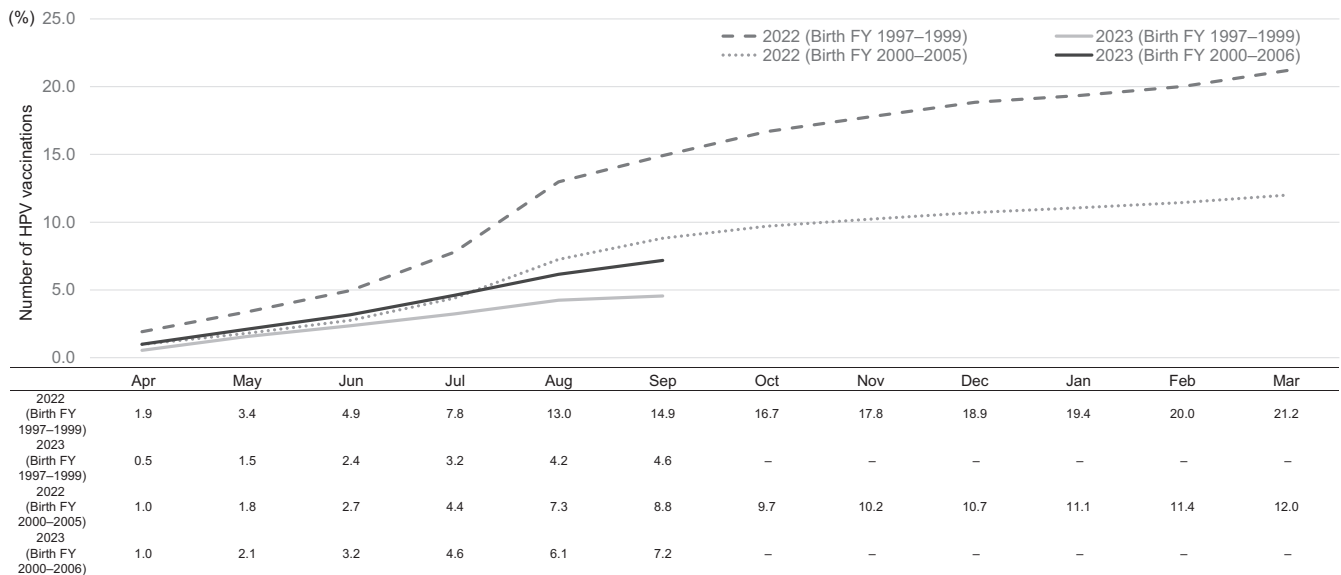


FIGURE 4 Cumulative HPV vaccine initial vaccination rate by catch-up vaccination among unvaccinated subjects at the beginning of each vaccination from FY 2022 to FY 2023 by generation.

vaccinations outside of one's municipality of residence and to increase publicity exposure.

We estimated that the vaccination rate in Japan would recover to ~40% after the resumption of the governmental full active recommendation for HPV vaccination.¹⁰ In the present analysis, we presented the latest vaccination rates. However, we do not consider that a significant improvement can be expected. Japan is far from the WHO target of 90% in terms of the current vaccination situation.

This precipitous and extended gap in HPV vaccinations has predictably led to real harm,¹⁵ with an increase in high-risk HPV 16 and 18 infections and abnormal cervical cytology already reported among 20- and 21-year-olds.^{16,17} However, when compared with the inflammatory 2013 reports of suspected HPV

vaccination side effects, these reports of increasing impending cervical cancers are rarely mentioned by the same media today. That suggests a need to reconsider and demand better journalistic ethics.

In response to the COVID pandemic, the social media platform YouTube adopted a formal "medical misinformation policy" for content on health information. Freedom of the press must not be frivolously infringed; however, sometimes the press has forgotten that with freedom comes the heavy burden of responsibility to treat the truth with the ultimate respect over political stance, profit, or ego. This social responsibility is strongest for news reports regarding information that could significantly affect the medical health of the public.

The large-scale retrospective data-driven analysis reported Japan's confidence in the importance, safety, and effectiveness of vaccines was very low.¹⁸ Japan should have an unbiased system to evaluate the accuracy of such reports on medical issues. Although all sides of important medical issues should be heard, a nod toward the most factual should also be made. We need to create an organization similar to America's Centers for Disease Control and Prevention to help provide trustworthy medical advice and sources of further information. We should seek to establish a social communication system that can handle the accuracy and specific immediacy of emerging medical information. In the Japanese population, education for health information literacy and practical preventive actions is insufficient, and this is an initiative that should be promoted in the future.

The initial policy decision to suspend the governmental vaccination recommendations for HPV vaccination, and then the decision to continue that suspension for almost 9 long years, will almost certainly cause, for decades to come, significant increases in cervical cancer cases and deaths. Even after reaching this current stage of recommendation resumption and catch-up programming, the HPV vaccination rate in Japan is still in an abysmal state.

There are limits to our study. This report is not based on Japan's national data. The municipalities that provided data for this survey were more positive about providing their HPV vaccine information than other municipalities. These two municipalities were the first in the country to simultaneously distribute HPV vaccine information in schools starting in FY 2019 when the recommendation was still suspended by the national government. This suggests that nationwide immunization rates may be even lower than those shown in our limited study. However, the national data on HPV vaccination rates in Japan for FY 2023 are not yet available. The catch-up vaccination program is scheduled to end in March 2025. In order to provide an earlier update on the vaccination situation in FY 2023, data from an ordinance-designated city and a core city were used.

The government's suspension of its HPV vaccination recommendations for nearly 9 years has caused significant harm to Japan's cervical cancer control efforts. For multiple reasons, Japan has been unable to establish a nationwide HPV immunization database. Japan's government, media, medical and educational institutions, and vaccination targets (now both boys and girls) and their parents need to squarely recognize the reality that HPV vaccination rates are at crisis-low levels. We must substantially elevate public awareness of cervical cancer prevention and cervical screening among all at-risk individuals. We must redouble our efforts to do so, or risk a national cervical cancer catastrophe.

AUTHOR CONTRIBUTIONS

Asami Yagi: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; software; validation; visualization; writing – original draft. **Yutaka Ueda:** Conceptualization; funding acquisition; investigation; methodology; project administration; resources; validation; writing – review and editing. **Emiko Oka:** Methodology; writing – review and editing.

Satoshi Nakagawa: Conceptualization; methodology; writing – review and editing. **Tadashi Kimura:** Supervision. **Koichiro Shimoya:** Conceptualization; supervision.

ACKNOWLEDGMENTS

We would also like to thank Dr. G.S. Buzard for his constructive critique and editing of our manuscript.

FUNDING INFORMATION

A Health and Labour Sciences Research Grant (23EA1002) from the MHLW supported this research.

CONFLICT OF INTEREST STATEMENT

AY and YU have each previously received a lecture fee from Merck Sharp & Dohme (MSD). The remaining authors declare no conflict of interest.

ETHICS STATEMENTS

Approval of the research protocol by an institutional reviewer board: This study was approved by the Ethics Committee of the Osaka University Hospital. Informed consent: N/A. Registry and registration number of the study/trial: N/A. Animal studies: N/A.

ORCID

Asami Yagi  <https://orcid.org/0000-0002-3222-5963>

Yutaka Ueda  <https://orcid.org/0000-0001-8760-6379>

REFERENCES

1. Singh D, Vignat J, Lorenzoni V, et al. Global estimates of incidence and mortality of cervical cancer in 2020: a baseline analysis of the WHO global cervical cancer elimination initiative. *Lancet Glob Health*. 2023;11:e197–e206. doi:10.1016/S2214-109X(22)00501-0
2. Hall MT, Simms KT, Lew JB, et al. The projected timeframe until cervical cancer elimination in Australia: a modeling study. *Lancet Public Health*. 2019;4:e19–e27. doi:10.1016/S2468-2667(18)30183-X
3. Cervical Cancer, the World Health Organization. https://www.who.int/health-topics/cervical-cancer#tab=tab_1
4. Report of the SAGE Working Group on Vaccines. <https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization>
5. Our World in Data. <https://ourworldindata.org/covid-vaccinations>
6. Simms KT, Hanley SJB, Smith MA, Keane A, Canfell K. Impact of HPV vaccine hesitancy on cervical cancer in Japan: a modeling study. *Lancet Public Health*. 2020;5:e223–e234.
7. Yagi A, Ueda Y, Kakuda M, et al. Epidemiologic and clinical analysis of cervical cancer using data from the population-based Osaka cancer registry. *Cancer Res*. 2019;79:1252–1259.
8. Tanaka S, Palmer M, Katanoda K. Trends in cervical cancer incidence and mortality of young and middle adults in Japan. *Cancer Sci*. 2022;113:1801–1807.
9. Nakagawa S, Ueda Y, Yagi A, Ikeda S, Hiramatsu K, Kimura T. Corrected human papillomavirus vaccination rates for each birth fiscal year in Japan. *Cancer Sci*. 2020;111(6):2156–2162. doi:10.1111/cas.14406
10. Yagi A, Nakagawa S, Ueda Y, et al. Effectiveness of catch-up and routine program of the 9-valent vaccine on cervical cancer risk reduction in Japan. *Cancer Sci*. 2023;115:916–925. doi:10.1111/cas.16055

11. Ministry of Health, Labour and Welfare: The 23rd Welfare Science Council Vaccination and Vaccine Subcommittee Side-Reaction Study Group. 2016. (In Japanese). <https://www.mhlw.go.jp/file/05-Shingikai-10601000-Daijinkanboukouseikagakuka-Kouseikagaku/0000147016.pdf>
12. The "Report on Regional Public Health Services and Health Promotion Services" published by MHLW. (In Japanese). <https://www.e-stat.go.jp/>
13. National Population Census. (In Japanese). <https://www.stat.go.jp/data/kokusei/2020/kekka.html>
14. Ministry of Health, Labour and Welfare: The 94th Welfare Science Council Vaccination and Vaccine Subcommittee Side-Reaction Study Group. 2023. (In Japanese). <https://www.mhlw.go.jp/content/10601000/001126459.pdf>
15. Tanaka Y, Ueda Y, Egawa-Takata T, Yagi A, Yoshino K, Kimura T. Outcomes for girls without HPV vaccination in Japan. *Lancet Oncol*. 2016;17:868-869.
16. Sekine M, Yamaguchi M, Kudo R, et al. Suspension of proactive recommendations for HPV vaccination has led to a significant increase in HPV infection rates in young Japanese women: real-world data. *Lancet Reg Health West Pac*. 2021;16:100300.
17. Yagi A, Ueda Y, Ikeda S, et al. 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. *Lancet Reg Health West Pac*. 2021;18:100327.
18. de Figueiredo A, Simas C, Karafillakis E, Paterson P, Larson HJ. Mapping global trends in vaccine confidence and investigating barriers to vaccine uptake: a large-scale retrospective temporal modelling study. *Lancet*. 2020;396(10255):898-908. doi:10.1016/S0140-6736(20)31558-0

How to cite this article: Yagi A, Ueda Y, Oka E, Nakagawa S, Kimura T, Shimoya K. Even though active recommendation for HPV vaccination has restarted, Japan's rates have not recovered. *Cancer Sci*. 2024;00:1-7. doi:10.1111/cas.16167