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RESEARCH

Imprecision in adverse event reports following immunization against HPV in Japan and COVID-19 in the USA, UK, and Japan—and the effects of vaccine hesitancy and government policy

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Abstract

Introduction Erroneous reports of adverse events following immunization (AEFIs) likely exacerbated the 2013 collapse of Japan's HPV immunization program. A similar phenomenon characterized the first months of COVID-19 immunization programs in the USA, UK, and Japan with high rates of reported anaphylaxis. These reports illustrate the susceptibility of supposedly objective medical judgments to public anxiety.

Purpose and methods This study documents inaccuracies in reported AEFIs using three quantitative methods.

Results One of these quantitative methods revealed that false-positive rates for anaphylaxis reports following HPV and later COVID-19 vaccination ranged from 74 to 91 percent. However, unlike HPV vaccinations in Japan, anaphylaxis reports following COVID-19 vaccines fell in Japan, the USA and the UK in the latter months of 2021. Nevertheless, false-positive rates for anaphylaxis reports remained high, suggesting a high degree of imprecision in serious AEFI reports from many countries for many vaccines. Japan's HPV immunization program indicates that media reports, patient hesitancy, healthcare providers' perspectives on vaccine safety, and consistency of government messaging, all influence report number and accuracy. A parallel publication analyzes in depth how such factors affect AEFI reports.

Conclusion Confidence in the safety of the COVID-19 vaccines may have been bolstered trough rapid monitoring of AEFI reports and communication of these findings. This may partly explain the different trajectories of serious AEFI following HPV immunizations in Japan and COVID-19 immunizations in the USA, UK, and Japan.

Keyword Erroneous reports · Adverse events (AEs) · False positive · Timing of reports · Serious/non-serious AE · Anaphylaxis · AE reporting system

Introduction

Widespread immunization against COVID-19 is important to prevent its spread. Thus, coping with vaccine hesitancy globally is vital to protect public health. While cases of serious adverse events (AEs) following COVID-19 immunization have been reported, assessing the accuracy of these reports is important to determine the safety of these vaccines and to decrease vaccine hesitancy.

The curtailment of Japan's HPV immunization program due to widespread concerns about vaccine safety serves as a warning about the dangers of vaccine hesitancy for COVID-19 immunization programs. Our research has shown that false-positive rates among AE reports designated as serious are high for vaccines generally [1]. This imprecision was particularly pervasive in serious AE reports following HPV immunizations in Japan. The Japanese HPV immunization program was marked by widespread public and media concern about safety and by wavering government support [2]. As demonstrated below, these factors influenced the supposedly objective professional judgments of healthcare providers (HCPs). False-positive reports appeared so frequently that the AE data likely contributed to the perception that the HPV vaccinations were unsafe. Since 2015, few Japanese adolescents have been immunized against HPV, and the health consequences are likely to be severe.

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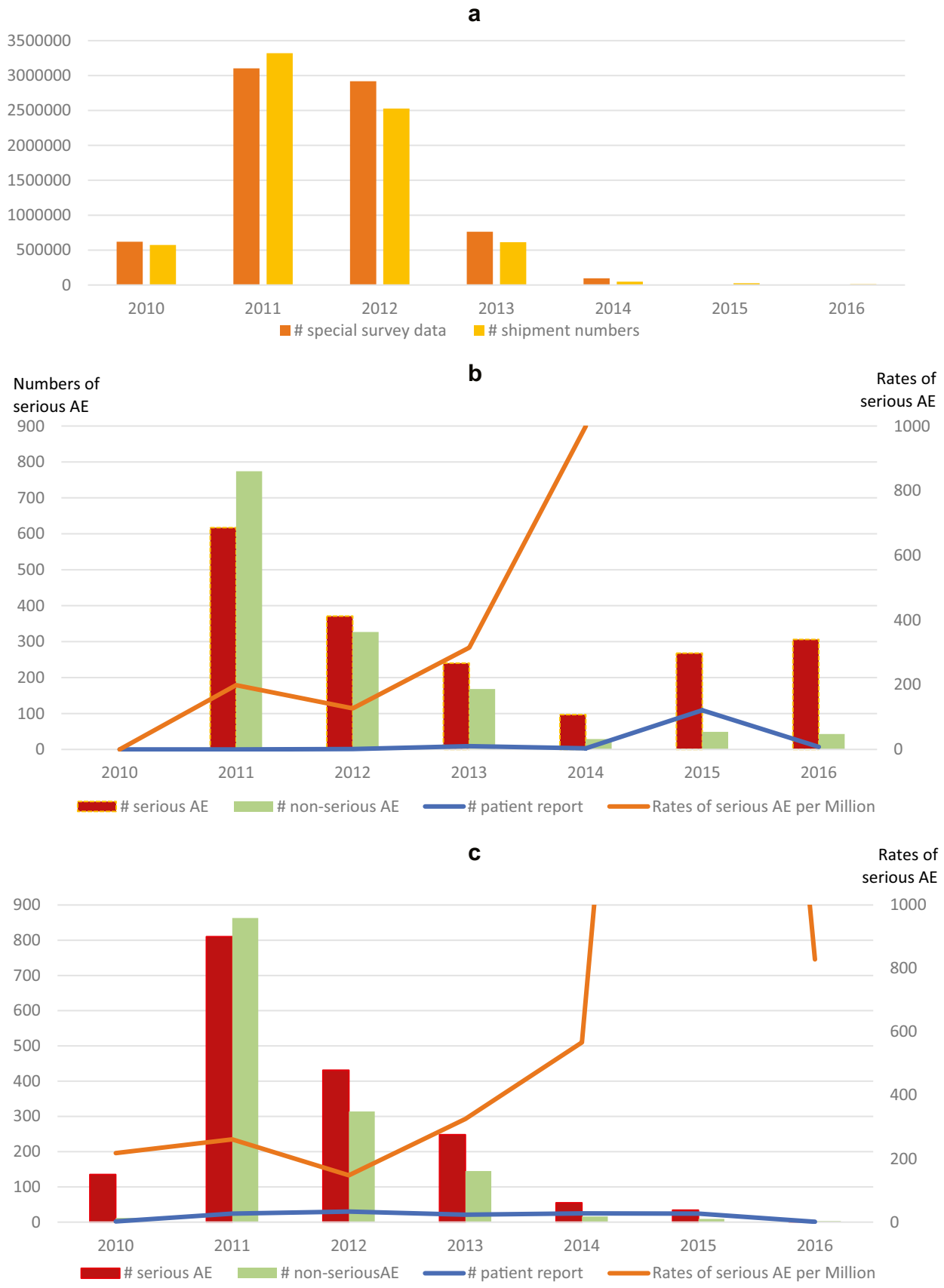
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◂**Fig. 1** **a** Numbers of Japanese HPV immunizations by year and special survey data vs shipment numbers. **b** Japanese AE reports following HPV immunizations (by serious vs non-serious and the year of VARRC review). **c** Japanese AE reports following HPV immunizations (by serious vs non-serious and the year of AE onset)

Now, as mass vaccination campaigns against COVID-19 are underway globally, public concerns about safety have also led to widespread vaccine hesitancy in many regions. Anaphylaxis rates are among the leading objective indicators of vaccine safety. Here we report on changes in anaphylaxis reporting rates following COVID immunizations in the USA, UK, and Japan and compare these with rates of anaphylaxis and other serious AEs following HPV immunization at the height of Japan's HPV immunization program. We show that rates of anaphylaxis following COVID vaccinations decreased over 6 months from March to September 2021 as vaccination programs ramped up, in contrast to the trend following the beginning of the HPV immunization campaign in Japan in 2010 when rates of anaphylaxis and other serious AEs increased. Nevertheless, false-positive rates of these reports remained high for both vaccines. The contrast between the trends in anaphylaxis rates for the two vaccines offers clues as to circumstances that influence serious AE reporting rates, while the persistently high false-positive rates offer insights into more intractable limitations on the accuracy of these reports.

Background

Japan's HPV immunization program

With an age-adjusted incidence rate of about 15 per 100,000, Japan's cervical cancer incidence rate is among the highest in developed countries [3, 4]. Particularly concerning is the relatively high and increasing incidence among young women ages 15–44 (crude rate 22.4 per 100,000 in 2018) [5–7]. Low rates of cervical cancer screening, especially among young women, increase the risk of cervical cancer onset and mortality [8].

HPV vaccines were first approved outside Japan in 2006 [6]. Japan's Ministry of Health, Labour and Welfare (MHLW) approved GSK's Cervarix® in October 2009 and MSD's Gardasil® in July 2011. Three doses were recommended for both vaccines. MHLW launched an urgent campaign to promote the vaccination of girls in grades 7–10 (ages 12–16) with the eventual goal of immunizing all girls in a single 12-month birth cohort at about age 12 [9]. By 2010, a combination of national and regional government funding covered the cost of the vaccine in most regions. More than 70% of girls born in each of the years 1996–1999 likely received the full series. Even about half of girls born in 1994 and 1995 received at least one dose [10, 11]. In April 2013, the vaccines were included in Japan's National Immunization Program (NIP) meaning they would be provided free of charge [12].

Prior to March 2013, Japanese media coverage of the HPV vaccine was either positive or neutral. However, that month, one of Japan's leading newspapers published a report describing the pain, progressive numbness, weakness, sleep difficulties, and problems with cognition, experienced by a junior high school student soon after immunization and continuing for over a year [2]. Suddenly media reports swung sharply against the vaccine and increased in frequency. Many described cases of movement disorders and memory disturbances in addition to various pains [13–15]. Patient organizations began media campaigns against the vaccines, some claiming that pain and other disorders can occur up to several years following immunization [16].

On 13 June 2013, WHO's Global Advisory Committee on Vaccine Safety (GACVS) issued an update affirming the safety and efficacy of the vaccines followed by a similar statement in September from the International Federation of Gynecology and Obstetrics [17]. Case control studies conducted in the latter half of 2015 nationally and in the city of Nagoya would show that the diverse symptoms associated with the vaccine occurred just as frequently among unimmunized adolescent girls as among those immunized [10, 18, 19].

Nevertheless, one day after the GACVS statement, MHLW suspended its proactive recommendation that adolescent girls be vaccinated against HPV based on high rates of pain after the immunization, though the vaccines remained in the NIP and thus available free of charge [20]. Before the 2013 suspension, Japan's Vaccine Adverse Reactions Review Committee (VARRC) publicized rates of serious adverse events following immunization (SAEFI) for Cervarix (43.3 per million doses) and Gardasil (33.2 per million doses) and compared these with those of other routinely administered vaccines, which ranged from 2.3 to 27.5 per million doses. The SAEFI rate of Gardasil and Cervarix combined was 41.3 per million, two to ten times higher than for the other vaccines. The vote to suspend was divided, with three of the MHLW VARRC members insisting that the proactive recommendation be suspended and two voting for its continuation. One committee member rationalized the suspension as leaving the vaccination decision up to the adolescent and her family, without interference from the Government [21].

Immunizations plummeted as shown in Fig. 1a. By mid-2014, less than 1% of eligible girls were being immunized [6, 22]. Only 1.6% of women born in 2001 received even a single dose and fewer than 0.5% of women born in subsequent years [10]. Finally in November 2021, the VARRC agreed unanimously to reinstate the proactive recommendation [23].

Histological results from cervical screens of women born 1991 to 1993 (pre-vaccination) compared to those born 1994–1996 (largely immunized) show significantly lower prevalence in the largely vaccinated cohort not only of atypical squamous cells of undetermined significance (the most common Pap test abnormality and almost always a sign of HPV infection) but also precancerous high-grade cervical intraepithelial neoplasia (CIN) [24]. Unless vaccination restarts soon, 3400 to 3800 preventable cases and 700 to 800 preventable deaths will occur among women born each year following 2000 [6].

Unfortunately, physicians were negatively influenced by media reports and the government's response. Among 264 obstetricians and gynecologists who responded to a 2014 survey, 56 had daughters eligible between 2012 and 2014 to receive an HPV vaccine. By the end of 2012, most had had their eligible teenage daughters immunized. But following MHLW's June 2013 suspension of its proactive recommendation, none had had any of their eligible daughters immunized. The most common reason cited was media reports of adverse effects. Nevertheless, over 60% of these specialists said the government should reinstate its proactive recommendation, and they recommend teenagers receive the vaccination [25]. A follow-up survey in 2017 showed that only a small proportion (5 of 31) of obstetricians and gynecologists with unvaccinated, eligible daughters had had them vaccinated. Yet over 70% of the 254 respondents said the government should reinstate its proactive recommendation, and they recommend HPV vaccination for teenagers [9]. Contrary to their own professional judgments, the way these physicians treated their families and patients was influenced by media reports and government hesitancy.

This paper aims to analyze the mistakes made by providers in reporting HPV AEs, determine to what extent they were also made in the early stages of Japan's COVID immunization program, and suggest ways to prevent these mistakes in immunization programs worldwide.

Methods and data sources

Numbers of immunizations and AEs and the roles of VARRC

For HPV and COVID-19 vaccines, numbers of anaphylaxis reports were obtained from meeting materials of the VARRC convened by the MHLW [26, 27], the CDC website [28], and (COVID only) the website of the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) [29].

The Japanese VARRC materials include AE case reports and estimated vaccine shipment numbers, allowing estimation of AE incidence rates. Uniquely among SAEFIs, the VARRC reviews all anaphylaxis reports for all vaccines administered in Japan [1]. As described under Findings, these reviews determine which reports were true-positives, allowing comparison of true vs false-positive rates. Also as described below, using specially collected data on actual HPV immunization numbers, we confirmed that shipment data are a reasonable surrogate for actual shots administered.

Denominators to calculate US HPV AE incidence rates were estimated from US age-specific population and vaccination rates [1]. Covid vaccine anaphylaxis incidence rates for all countries were obtained from cited references.

The line items in the AE reports that VARRC reviews contain only the time of AE onset reported by patients. We have to infer the date patients informed providers of their AEs from the time these reports were submitted to VARRC, which can only be estimated by the time windows between VARRC meetings. In the case of HPV vaccines, the time between reported symptom onset and estimated reporting to HCPs and then VARRC was often over a year.

Classification as serious vs non-serious based on ICH criteria

ICH E2A guidelines require persons submitting AE reports to indicate whether the AEs were serious. These define a serious AE as one that results in death, is life-threatening, requires inpatient hospitalization or results in prolongation of existing hospitalization, results in persistent or significant disability/incapacity or a congenital anomaly/birth defect, or is a medically important event or reaction such as might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above [30]. Such AEs following immunization are referred to as SAEFIs.

Findings

Findings are presented first for Japan's HPV immunization program which began in 2010 and next for the COVID-19 immunization program in the USA, UK, and Japan that began in winter to spring 2021.

HPV immunizations and AE reports in Japan

Denominators to calculate AEs

We verified that shipment numbers are reasonable surrogates for administered vaccine doses using special MHLW survey data showing the proportion of girls nationwide who had received the first HPV dose and regional survey data on the likelihood that girls who received the first dose would then receive the second and third doses [1, 11, 31]. Figure 1a compares shipment numbers of the HPV vaccines each year with the estimated numbers of actual HPV vaccinations (shots). The difference of two estimates is within 6% of each other. Both

estimates show a rapid ramp up in immunizations between 2010 and 2011 to immunize girls in several birth cohort years, with this effort continuing in 2012 and then suddenly falling off in 2013 with barely any immunizations in subsequent years.

Analysis of Japanese HPV immunization data showing susceptibility of medical judgment to outside influences

Figure 1a shows the sharp decline in HPV immunizations beginning in 2013.

As a first quantitative way to analyze imprecision, Fig. 1b shows the transition of serious/non-serious AE reports. In 2011, the year of most immunizations, the rate of serious AE reports was about 200 per 1,000,000 immunizations. Furthermore, the HCPs submitting these reports were classifying as serious many medical conditions, such as syncope and anxiety, that are rarely regarded as serious [1]. A random sample of the most commonly administered vaccines in Japan in the pre-COVID era showed that only 30 percent of HPV AEFI reports classified as serious listed a medical condition normally regarded as serious. This compares with nearly 60 percent of AE reports classified as serious following other immunizations. Rates of serious AEs following HPV immunizations were over four fold the rate following any other vaccine in Japan and nine fold the rate following HPV immunizations in the USA [1].

A second way we quantified imprecision is the timing of AE onset relative to HPV immunization and the timing of AE reporting relative to AE symptom onset. Over 10% of serious AE reports submitted from 2011 through 2016 were for AEs that began more than 28 days after immunization. This proportion increased along with anxiety about the HPV vaccines. In 2013, 2014, 2015 and 2016, respectively, 20%, 40%, 20% and 60% of symptoms were reported as arising more than half a year following vaccination (Supplemental Table) -- well beyond the 28-day limit to attribute any AE an HPV vaccination [32]. It is not surprising that patients brought such complaints to HCPs. What is surprising is that HCPs reported them, either directly or via manufacturing authorization holders (MAHs), and they became part of normal AE statistics, without any easily noticed indication that the timing of such reports raised questions about validity.

Similarly, over 40% of serious reports overall were probably reported to HCPs more than four months after onset of AE symptoms. Again, this gap deteriorated over time as anxiety about the HPV vaccines grew. About 10, 30, and 50% of the 2011, 2012, and 2013 serious reports, respectively, were for AEs that the patients waited at least four months to report to their HCPs (Supplemental Table). This trend worsened even more in subsequent years. Figure 1b shows a rebound in the number of serious reports submitted in 2015 and 2016. However, when serious cases are attributed to the years in which they occurred rather than the year they were reported, no rebound is apparent (Fig. 1c). Quintile analysis shows that most of the reports submitted after 2013 describe AEs that arose before March 2013 (Supplemental Table).

While it may be surprising that patients brought such complaints to HCPs, it is even more surprising that HCPs reported them, either directly of via manufacturing authorization holders (MAHs) and they become part of AE statistics, without any easily noticed indication that the timing of such reports raised questions about their validity [32] .

The third way we quantified imprecision was false-positive rates derived from VARCC reviews. As inferred from Table 1, the total number of false-positive anaphylaxis cases following HPV immunizations from 2010 through 2016 exceeded the number of true-positive cases by more than fivefold, for a false positive rate of 81 percent.

The reported rates of anaphylaxis were much less than for serious AEs as a whole (Fig. 1b,c) which include many conditions besides anaphylaxis. The yearly incidence rates for most of these other serious AEs are unstable because of small numbers [1]. However, the VARRC-verified anaphylaxis rates in Table 1, roughly track the total serious AE rates shown in Fig. 1c.

Comparison of anaphylaxis reports following COVID-19 immunizations in USA, UK, and Japan—background and time trends in immunizations and anaphylaxis reports

We analyzed early time trends in AE reports for the first two COVID-19 vaccines approved in each of the UK, USA, and in Japan. The US FDA granted emergency use authorization

Table 1 Anaphylaxis cases following HPV vaccinations in Japan

	2010	2011	2012	2013	2014	2015	2016
Shipment numbers	574,286	3,320,357	2,527,500	612,784	48,426	26,000	11,670
No. of anaphylaxis reports (Pre-VARRC review)	10	27	12	2	2	0	0
Rate per 1 M	17	8.1	4.7	3.2	41	0	0
No. VARRC-verified anaphylaxis cases	1	5	2	2	0	0	0
Rate per 1 M	1.7	1.5	0.79	3.2	0	0	0

(EUA) for the mRNA Pfizer-BioNTech and Moderna vaccines in December 2020. FDA officially approved the Pfizer vaccine on 23 August 2021 [33, 34]. The UK's MHRA approved the Pfizer and Oxford/Astra Zeneca vaccines on 2 and 30 December, respectively [35] and the Moderna vaccine on 8 January 2021. The Japanese Pharmaceutical and Medical Device Agency (PMDA) approved the Pfizer vaccine on 14 February 2021 [36] and both the Moderna and Astra Zeneca vaccines on 21 May 2021. However, only since August 2021 has the Astra-Zeneca vaccine been used for mass immunization, and only for persons at least 40 years old, out of concern for thrombotic AEs [37, 38].

The upper half of Table 2 shows anaphylaxis report numbers in the UK, USA, and Japan from the first approval of any vaccine to one to three months later. As of 21 March 2021, 578,835 COVID-19 immunizations had been administered in Japan, all the Pfizer-BioNTech vaccine and almost all to health workers, PMDA had received 181 reports of associated anaphylaxis cases, for a rate of about 313 per million immunizations [29, 39]—about 18 times the rate of anaphylaxis following HPV vaccinations in 2010 (17 per million). The VARRC verified 47 of these anaphylaxis cases for a rate of 81 per million doses and a false-positive rate of 74 percent. In contrast, CDC reported that, as of 23 December, 1.8 million doses of the Pfizer vaccines had been administered in the USA. One hundred seventy-five anaphylaxis reports were received, but only 21 satisfied Brighton criteria, for a rate of verified anaphylaxis of 11 per million and a false-positive rate of 87% [28]. UK data compiled as of 14 March showed 563 anaphylaxis or anaphylactoid reactions (not verified according to Brighton criteria) associated with 25.9 million doses of the Pfizer and Astra-Zeneca vaccines (21.7 per million) [29]. The early US COVID-19 vaccine anaphylaxis rate (11 per million) was two orders of magnitude higher than the average US anaphylaxis report rate for nine other routinely administered vaccines (0.1 per million) [1].

Roughly half a year later as the COVID immunization programs in all three countries ramped up, rates of anaphylaxis reports decreased. In Japan as of 12 September 2021, the cumulative anaphylaxis rate for the Pfizer vaccine was 21 per million doses (3.9 per million for cases that VARRC determined met Brighton criteria) and 17 per million (1.5 per million for verified cases) for the Moderna vaccine [40]. These data are for reports submitted from the MAHs only and do not include reports submitted directly from (HCPs, which constitute roughly 45% of anaphylaxis reports for vaccines generally in Japan [1]). However, separate data show that anaphylaxis cases reported by HCPs also decreased substantially [41].

The verified Japanese anaphylaxis rates are now lower than those in the USA, where the rate of cases that satisfied

Table 2 Anaphylaxis case reports and rates per million COVID-19 vaccine doses over time in the USA, UK, and Japan4

		USA	UK	Japan
First assessment	Data as of	23 December 2020	4 March 2021	21 March 2021
	Vaccines used as of date	Pfizer (100%)	Pfizer and AZ (no market share available)	Pfizer (100%)
	Doses to the date	1,893,360	25,900,000	578,835
	Reported cases	175*	563	181
	Verified anaphylaxis	21	N/A	47
	Incidence rate (per million)	92	22	313
	Verified incidence rates (per million)	11	N/A	81
	% false positive	88%	N/A	74%
Second assessment	Cumulative data as of	21 June 2021	22 September 2021	12 September 2021
	Vaccines used as of date	Pfizer (58%) and Moderna (42%)	Pfizer (45%), Moderna (52%), and AZ (2%)	Pfizer (84%) and Moderna (16%)
	Doses to the date	11,845,128	93,200,000	146,236,674
	Reported cases	183	1344***	2925
	Verified anaphylaxis	55	N/A	509
	Incidence rate (per million)	15	14	20****
	Verified incidence rates (per million)	5	N/A	3****
	% false positive	68%**	N/A	83%****

*Identified for further review as possible cases of severe allergic reaction, including anaphylaxis

**171 out of 183 underwent full review

***In the UK, the incidence rates per million were 12 for Pfizer, 17 for AZ, and 15 for Moderna

****In Japan, the incidence rates per million were 21 (4 verified) for Pfizer and 17 (1.5 verified) for Moderna, while the false-positive rates for these reports were 81% for Pfizer and 91% for Moderna

Brighton criteria were 4.8 and 5.1 per million doses for the Pfizer and Moderna vaccines, respectively, as of 21 June 2021 [42]. In the UK as of 22 September 2021, unverified rates were 12 per million doses of the Pfizer vaccine, 15 per million doses of Moderna, and 17 per million doses of Astra Zeneca [43].

Although anaphylaxis report rates have decreased in all countries, they are higher than those for commonly administered adult vaccines in Japan and the USA by an order of magnitude, and false-positive rates among the anaphylaxis reports remain high. The Japanese false-positive rate for the Pfizer and Moderna vaccines combined increased from 74% in March 2021 to 83% in September 2021. The US false-positive rate for the Pfizer and Moderna vaccines combined was 68%.

However, these false-positive rates for COVID vaccines in the USA and Japan are similar to false-positive rates for many other common vaccines administered in Japan in the pre-COVID era. About 70% of Japanese anaphylaxis reports across nine common vaccines (not just HPV) were false positives [1]. This suggests that false-positive rates for many serious AEs may be high in many countries.

Available data specific for age and gender suggest that the highest rates of verified anaphylaxis following COVID immunization were among relatively young women: 18 per million doses for women ages 20–29, 23 per million for ages 30–39, and 18 per million for ages 40–49, compared with 7 per million for women overall and only 1.2 per million for men overall. For the youngest age group, ages 10–19 (the one most comparable to the teenage girls who received HPV immunizations a decade earlier), the rate was only 3 per million. However, vaccination of children had only begun when data were collected in August 2021. Only about 0.75 million had been vaccinated compared with over 4 million ages 20–29, over 4 million ages 30–39, and over 7 million ages 40–49. Consistent with the last note for Table 2, this pattern of high anaphylaxis rates for relatively young women was more pronounced with the Pfizer than the Moderna vaccines [44].

For 10-year age groups, false-positive rates for anaphylaxis reports ranged from 79 to 89%. There was no suggestion that these rates were higher among the younger age ranges where women showed high rates of anaphylaxis. These false-positive rates were 84%, 79% and 80% for vaccines in their 20 s, 30 s and 40 s, respectively. Moreover, these rates did not differ markedly by gender.

As mentioned above, anaphylaxis rates may be only an approximate surrogate for the totality of serious AE reports following immunizations. However, currently the only AE for which we can compare COVID-19 AE report rates across countries, and for which we have data on validity, is anaphylaxis.

Discussion

Available data suggest worrisome similarities between rates of anaphylaxis reports at the beginning of the Japanese HPV immunization program in 2010 and the initial stages of the global COVID immunization program in 2021. Reported rates of anaphylaxis were higher following COVID immunizations (pre-verified: 22–313 per million doses; VARRC verified: 11–81 per million doses) compared to the first 2 years of Japan's HPV immunization program (pre-verified: 8–17 per million doses; verified: 1.5 to 1.7/M). False-positive rates for these reports are about 80% in both instances (Tables 1 and 2).

Our analysis of Japan's HPV immunization program provides clues to factors that influence high rates of serious AEFI reports and high false-positive rates among these reports. Vaccine hesitancy is one such factor. A 2016 survey ranked Japanese lowest among Asian populations in terms of confidence in vaccine safety, with 31% of respondents disagreeing with the statement, "Overall I think vaccines are safe." (However, France and some other European countries had even lower confidence in vaccine safety [45].) Early in 2021, Japanese vaccine hesitancy rates were high with 11% of the population indicating negative attitudes about the COVID vaccines [46]. The history of Japan's HPV program shows how vaccine hesitancy, combined with negative publicity and government hesitancy, can sway professional judgment to produce inaccurate AEFI, which in turn probably contributes to negative perceptions towards vaccination among medical professionals and the public.

Rates of overall serious AEs following HPV immunizations in Japan were very high, even in the first years of that program 2010–2012 (Fig. 1b, c). Although we do not have comparative data for COVID vaccine programs, we know that the proportion of HPV vaccine AE reports that the reporters classified as serious and that listed a medical condition that normally is regarded as serious was lower than for other vaccines. Furthermore, the rates of serious AEs following HPV immunizations in Japan were much higher than rates of serious AEs reported following HPV immunizations in the USA or following other immunizations in Japan [1]. Our analyses of the actual seriousness of AEs listed as serious, and of the timing of alleged AE symptoms and reporting, provides circumstantial evidence that Japanese physicians were doubtful about the validity of the AEs they and were reporting. Alternatively, they may have been influenced by an already widespread undercurrent of public skepticism regarding these vaccines and perhaps by reports of AEs from colleagues, and these negative factors may have influenced their reports. If either of these possibilities were at play, authoritative statements and analyses from

government and scientific agencies may have reduced the frequency of dubious AEs and helped salvage the program.

However, our parallel research into AE rates following other pre-COVID vaccines suggests that imprecision in AE reporting characterizes all vaccines [1]. This likely reflects general, systemic problems with AEFI reporting. Disentangling imprecision that characterizes AE reports for vaccines generally, from imprecision that is unique to a controversial vaccine such as HPV and COVID, is not straightforward. Certain aspects of imprecision are unique to the Japanese HPV AEs. The extent to which these unique aspects also apply to COVID vaccines increases the danger that similar problems may befall COVID programs. First, reported HPV anaphylaxis rates were higher than for any other Japanese vaccine, and false-positive rates among these reports were higher than for most of the other eight Japanese vaccines we analyzed [1]. Since early COVID anaphylaxis rates were higher than, and false-positive rates were at least as high as, the Japanese HPV rates, COVID AE rates may indeed be uniquely high and their reliability relatively low, as was the case for Japanese HPV AEs. Another indicator of imprecision that was unique to Japanese HPV immunizations is the large proportion (70%) of Japanese HPV AE reports that were designated as serious but listed only conditions generally regarded as non-serious. However, we do not know if the same phenomenon applies to serious COVID AE reports. As for the large proportions of serious HPV AE reports that were dubious in terms of either the delay between immunization and AE onset or the delay between AE onset and reporting to HCPs, we lack data indicating the extent to which they apply to other vaccines [1].

Nevertheless, certain data trends, as well as differences in government approaches, suggest that the trajectories of AE reports for COVID and Japanese HPV vaccines likely will be different. Most importantly, as shown in Table 2, incidence rates of anaphylaxis AE reports decreased from about 22–313 per million doses (pre-verified) to 14–20 per million doses (pre-verified) from the first 2–3 months of each country's immunization program to about half a year after the beginning of these programs.

Also, government support of the vaccinations has been much stronger than for the HPV vaccines, and since May 2021, numerous sites across Japan have offered the Pfizer or Moderna vaccines for free. As for Japan's relatively high level of vaccine skepticism, the fact that Japan now ranks among the highest countries in terms of the percentage of its population that is full vaccinated [47] indicates that skepticism can be overcome, in part through government policies.

The VARRC and MHRA are rapidly updating and publicizing data on numbers of anaphylaxis reports and the proportion that meet recognized diagnostic criteria [48, 49]. Such up-to-date information gives providers and the public real-time understanding about the actual risks associated with COVID vaccines.

On the other hand, persistently high rates of false-positive anaphylaxis reports across many vaccines (and high Japanese false-positive rates of Guillain Barre and acute demyelinating encephalomyelits that we analyze elsewhere [1]) suggest systemic imprecision affecting AE reports for all vaccines. The recognized diagnostic criteria for anaphylaxis are those developed by the Brighton Collaboration Anaphylaxis Working Group in 2007. To illustrate how these criteria work, a child whose parent said she developed a hoarse voice, abdominal pain, and either itchy eyes or a general prickly sensation following immunization would likely satisfy Brighton Level 3 criteria [50]. Nevertheless, for each of the nine common vaccines we analyzed in our parallel research, at least half of the anaphylaxis AEs failed to meet even Brighton Level 3 criteria. This indicates that HCPs often assign the anaphylaxis diagnosis loosely [1].

To some extent, this might be a uniquely Japanese problem, because Japanese AE reporting forms list individual AEs for each vaccine which the HCP (or MAH) must check to indicate occurrence [32]. Anaphylaxis is always listed first so there may be a tendency for busy providers to simply check the first AE they see. However, this would not explain the equivalently high anaphylaxis rates for COVID vaccinations in the USA, where AE reports are entered free-form without a checklist.

Japanese HCPs must report any reportable AEs when the AE occurs within specific time intervals as indicated in the reporting form. When reportable AEs occur after the time interval, they should be reported if the reporter considers that the vaccine's association cannot be ruled out [32]. Similarly, US HCPs are required to report any reportable AEs within the specified time period after vaccinations and encouraged to report any AEs that occurs after the specified time period [51]. MAHs are required to transmit to regulatory authorities all serious AEs that come to their attention, and MAHs's main information source are HCPs. Our findings suggest that many HCPs accept at face value the claims of patients regarding the type and severity of their reactions, and MAHs defer to these reports from HCPs. Thus, dubious AEs that do not meet standard diagnostic criteria or whose timing makes them suspect often are reported by HCPs and MAHs.

Despite all these reasons that serious AEs in general, and anaphylaxis reports in particular, should be viewed with caution, initial COVID vaccine AE reports show a trend towards relatively high rates in younger women. While it is possible that a combination of the factors mentioned above can account for this phenomenon, a biologic basis cannot be ruled out.

Conclusion

Japan's HPV experience shows that public concerns can influence medical judgments related to AEs, and it serves as a warning how such pressures can overwhelm an important public health program. The decision of the Government to suspend the "proactive recommendation for HPV vaccination" could be the result of paying respect to public concerns; however, this decision may have worked unintentionally and ironically to raise concern among the public and medical community and increased vaccine hesitancy. The reaction also shows how AE reporters and vaccines are sensitive to government pronouncements and how ambiguous policies can have long-lasting negative effects. In contrast since the spring of 2021, the support of government (at least on a national level) for COVID-19 immunization has been strong in all three countries. Indeed, early 2021 witnessed a shift in government policy in both the USA and then Japan towards firmer support for vaccinations, along with companies recommending vaccination for their employees. It is plausible that this helped to reduce both vaccine hesitancy and the rate of serious AE reports in Japan, though similar effects in the USA may be less likely. However, neither the Japanese Government, nor most Japanese employers and schools, have mandated COVID vaccinations.

When HCPs and MAHs file reports, perhaps there should be a clear distinction between the symptoms that patients report and the objective observations of the examining HCP and his/her diagnoses. Reports could then be analyzed both according to diagnosis and severity based upon patients' reports and diagnosis and severity based upon the providers' assessments.

Making public the assessments of validity of aggregated AE reports, as is done for VARRC reports, may increase public confidence in vaccines, provide feedback to HCPs and MAHs, and provide a tool for assessing AEFI reporting systems worldwide. Government committees like VARRC should include a public communications expert who should help shape announcements about vaccine safety.

Finally, the possibility that age and gender differences might influence susceptibility to anaphylaxis follow immunization should be investigated.

As we enter an era where immunizations are the best way out of a global pandemic and where we face the prospect of periodic re-immunizations, scientifically sound policy toward immunization based on scientific evidence is important for the lives of millions.

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Declarations

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References

1. Inokuma I, Kneller R (n.d.) Features in vaccine adverse event reporting generated through the system: insights from the Japanese and U.S. reporting systems, in preparation
2. Asahi-shimbun (2013) Serious adverse event reported following HPV vaccination to junior high school students. https://www.asahi.com/area/tokyo/articles/MTW1303261300002.html. Accessed Nov 2022
3. Arbyn M et al (2020) Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. Lancet Glob Health 8(2):e191–e203
4. Cancer Today – IARC (2020) Estimated number of new cases in worldwide, both sexes, all ages. https://gco.iarc.fr/today/online-analysis-table. Accessed Nov 2022
5. ICO/IARC (2019) Information centre on HPV and cancer, Human papillomavirus and related diseases report. https://hpvcentre.net/statistics/reports/JPN.pdf
6. Simms KT et al (2020) Impact of HPV vaccine hesitancy on cervical cancer in Japan: a modelling study. Lancet Public Health 5(4):e223–e234. https://doi.org/10.1016/S2468-2667(20)30010-4
7. Motoki Y et al (2015) Increasing trends in cervical cancer mortality among young Japanese women below the age of 50 years: an analysis using the Kanagawa population-based Cancer Registry, 1975–2012. Cancer Epidemiol 39(5):700–706
8. Morimoto A et al (2015) Effect on HPV vaccination in Japan resulting from news report of adverse events and suspension of governmental recommendation for HPV vaccination. Int J Clin Oncol 20(3):549–555
9. Sawada M et al (2018) HPV vaccination in Japan: results of a 3-year follow-up survey of obstetricians and gynecologists regarding their opinions toward the vaccine. Int J Clin Oncol 23(1):121–125
10. Ministry of Health, Labour and Welfare, A joint meeting of the Vaccine Adverse Reactions Review Committee (VARRC) (2016) https://www.mhlw.go.jp/file/05-Shingikai-10601000-Daijinkanboukouseikagakuka-Kouseikagakuka/0000147016.pdf. Accessed Nov 2022
11. Hanley SJ, Sharon JB et al (2015) HPV vaccination crisis in Japan. The Lancet 385(9987):2571
12. Ministry of Health Labour and Welfare (2010) Special urgent grant to enhance HPV vaccine etc. https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou28/pdf/vaccine_kouhukin_enchou.pdf, Accessed Nov 2022
13. Tsuda K et al (2016) Trends of media coverage on human papillomavirus vaccination in Japanese newspapers. Clin Infect Dis ciw647
14. Okuhara T et al (2019) Newspaper coverage before and after the HPV vaccination crisis began in Japan: a text mining analysis. BMC Public Health 19(1):770
15. WORLD HEALTH ORGANIZATION et al (2013) GACVS safety update on HPV vaccines. https://www.who.int/vaccine_

safety/committee/topics/hpv/130619HPV_VaccineGACVSstatement.pdf. Accessed Nov 2020
16. National Attorneys Assocication for the HPV Vaccines Lawsuits in Japan (2013) http://hpv-yakugai.net. Accessed Nov 2022
17. Denny L et al (2013) Safety of HPV vaccination: a FIGO statement. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 123(3):187–188
18. The 23th Vaccination Sub-Committee Meeting (2016) Investigative Committee on Adverse Reactions, Health Sciences Council, Ministry of Health, Labour, and Welfare. (Also known as the Sobue Study.)
19. Hosono A (2018) No association between HPV vaccine and reported post-vaccination symptoms in Japanese young women: results of the Nagoya study. Papillomavirus Res 5:96–103
20. Ministry of Health, Labour and Welfare, Corresponding to the routine vaccination of HPV vaccine (recommendation) (2013) Health Service Bureau 0614–1, Director of Health Service Bureau. https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou28/pdf/kankoku_h25_6_01.pdf. Accessed Nov 2022
21. Ministry of Health Labour and Welfare (2013) Minutes of VARRC
22. Sekine M et al (2020) Japan's ongoing crisis on HPV vaccination. Vaccines 8(3):362
23. Ministry of Health Labour and Welfare (2021) Minutes of VARRC
24. Ministry of Health, Labour and Welfare, Q&A for COVID-19 vaccination. https://www.cov19-vaccine.mhlw.go.jp/qa/0053.html. Accessed Nov 2022
25. Egawa-Takata T et al (2016) Human papillomavirus vaccination of the daughters of obstetricians and gynecologists in Japan. Int J Clin Oncol 21(1):53–58
26. Vaccine Adverse Reactions Review Committee Meeting Material convened on (2018) https://www.mhlw.go.jp/file/05-Shingikai-10601000-Daijinkanboukouseikagakuka-Kouseikagakuka/0000199232.pdf. Accessed Nov 2022
27. Ministry of Health Labour and Welfare (2021) Summary of anaphylaxis cases following immunization against the new corona virus
28. Centers for Disease Control and Prevention (2020) Allergic reactions including anaphylaxis after receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine — United States, December 14–23. https://www.cdc.gov/mmwr/volumes/70/wr/mm7002e1.htm. Accessed Nov 2022
29. Medicines and Healthcare Products Regulatory Agency (MHRA) (2021) Coronavirus vaccine - weekly summary of Yellow Card reporting. https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting. Accessed Nov 2022
30. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use (1994) Clinical safety data management: definitions and standards for expedited reporting E2A
31. Nakagawa S et al (2020) Corrected human papillomavirus vaccination rates for each birth fiscal year in Japan. Cancer Sci 111(6):2156
32. Ministry of Health Labour and Welfare (2018) Form to report AEFI. https://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/saishin.pdf#search=%27%E5%89%AF%E5%8F%8D%E5%BF%9C+%E6%A7%98%E5%BC%8F%27. Accessed Nov 2022
33. Food and Drug Administration (2021) Comirnaty and Pfizer-BioNTech COVID-19 vaccine. https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/comirnaty-and-pfizer-biontech-covid-19-vaccine. Accessed Nov 2022
34. Food and Drug Administration (2021) Moderna COVID-19 vaccine. https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/moderna-covid-19-vaccine. Accessed Nov 2022
35. Medicines and Healthcare products Regulatory Agency (2020) Oxford University/AstraZeneca COVID-19 vaccine approved. https://www.gov.uk/government/news/uk-medicines-regulator-gives-approval-for-first-uk-covid-19-vaccine. Accessed Nov 2022
36. Ministry of Health Labour and Welfare (2021) Current R&D of Covid-19 vaccines. https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000121431_00223.html. Accessed Nov 2022
37. Ministry of Health Labour and Welfare (2021) Amendment of Administrative notice of COVID-19 vaccination (Directive)
38. Ministry of Health Labour and Welfare (2021) Administrative notice of system to vaccination and distribution of COVID-19 vaccine manufactured by AstraZeneca
39. IGUCHI, Toyotaka et al (2021) Cumulative adverse event reporting of anaphylaxis after mRNA COVID-19 vaccine (Pfizer-BioNTech) injections in Japan: the first-month report. Drug Saf 1–6
40. Ministry of Health Labour and Welfare (2021) Summary of anaphylaxis cases reported from Marketing Authorization Holders following immunization against the new corona virus
41. Ministry of Health Labour and Welfare (2021) Adverse Event Report from Healthcare Professionals based on Preventive Vaccination Act
42. Klein, Nicola P et al (2021) Surveillance for adverse events after COVID-19 mRNA vaccination. JAMA
43. Medicines and Healthcare Products Regulatory Agency (MHRA) (2021) Coronavirus vaccine - weekly summary of Yellow Card reporting
44. Ministry of Health Labour and Welfare (2021) VARRC meeting material 1–7–1: situation on AE reporting. https://www.mhlw.go.jp/stf/shingi/shingi-kousei_284075.html. Accessed Dec 2021
45. Larson HJ, de Figueiredo A, Zhao XH et al (2016) The state of vaccine confidence 2016: global insights through a 67-country survey. EBioMedicine 12:295–301. https://doi.org/10.1016/j.ebiom.2016.08.042. Accessed Mar 2021
46. Okubo R et al (2021) COVID-19 vaccine hesitancy and its associated factors in Japan. Vaccines 9(6):662
47. The New York Times (2021) Tracking coronavirus vaccinations around the world. https://www.nytimes.com/interactive/2021/world/covid-vaccinations-tracker.html. Accessed Nov 2022
48. Medicines and Healthcare Products Regulatory Agency (2021) Coronavirus (COVID-19) vaccines adverse reactions -a weekly report covering adverse reactions to approved COVD-19 vaccines. https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions. Accessed Nov 2022
49. Ministry of Health, Labour and Welfare (2021) VARRC meetings. https://www.mhlw.go.jp/stf/shingi/shingi-kousei_284075.html. Accessed Dec 2021
50. Gold MS, Gidudu J, Erlewyn-Lajeunesse M, Law B, Brighton Collaboration Working Group on Anaphylaxis (2010) Can the Brighton Collaboration case definitions be used to improve the quality of Adverse Event Following Immunization (AEFI) reporting? Anaphylaxis as a case study. Vaccine 28:4487–4498
51. Vaccine adverse event reporting system report an adverse event to VAERS (n.d.) https://www.vaers.hhs.gov/reportevent.html. Accessed Dec 2021