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Association between seasonal influenza vaccines and the increased risk of acute disseminated encephalomyelitis, estimated using the Vaccine Adverse Event Reporting System

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Acute disseminated encephalomyelitis (ADEM) is a rare and immune-mediated inflammatory disorder of the central nervous system (CNS) that can be triggered by infections and vaccinations. To date, only anecdotal case studies have reported the association between ADEM incidence and seasonal influenza vaccines, and multiple studies have found no association. This study aimed to investigate the association between the incidence of ADEM and seasonal influenza vaccines in a real-world setting using data from the United States Vaccine Adverse Event Reporting System (VAERS). Further, propensity score matching and disproportionality analysis was performed by calculating the adjusted reporting odds ratio (ROR) of reported ADEM cases associated with seasonal influenza vaccines using multiple logistic regression. Additionally, we analysed the time-to-onset using Weibull shape parameters (WSPs). The VAERS database contained 390,352 adverse events reported from January 2011 to December 2020. The ROR of seasonal influenza vaccines for ADEM was 3.02 (95% confidence interval: 1.72–5.33). The median duration (interquartile range) of ADEM was 11.0 (5.0–33.0) days. The median duration of ADEM induced by egg culture-based influenza vaccine (Egg-based vaccine) and cell culture-based influenza vaccine (Cell-based vaccine) was 10.0 (5.0–24.0) and 91.0 (79.0–125.0) days ($P < 0.001$), respectively. Only Cell-based cases had WSP $\beta > 1$, indicating a wear-out failure type. The incidence of ADEM within 30 days after administration of egg- and Cell-based vaccines was 78.6% and 0.0%, respectively. Our findings indicate that ADEM incidence is associated with seasonal influenza vaccines; thus, careful monitoring of ADEM is required within the first month of Egg-based vaccination and after two months of Cell-based vaccination. Neurologists and general practitioners should exercise caution, as the timing for careful monitoring varies depending on the vaccine type.

1. Introduction

Acute disseminated encephalomyelitis (ADEM) is a rare and immune-mediated inflammatory disorder of the central nervous system (CNS), which can be triggered by infections and vaccinations (Tenembaum et al. 2007; Stüve and Zamvil 1999; Bennetto and Scolding 2004). The systemic symptoms of ADEM, including fever, malaise, myalgia, headache, nausea, and vomiting, often precede the neurologic symptoms (Tenembaum et al. 2007; Stüve and Zamvil 1999; Bennetto and Scolding 2004). Post-vaccination ADEM often develops within one month after vaccination (Tenembaum et al. 2007; Stüve and Zamvil 1999; Bennetto and Scolding 2004), and the onset of symptoms varies depending on the vaccine type (Bennetto and Scolding 2004).

Most publications on this subject are anecdotal case reports (Huynh et al. 2008; Shoamanesh and Traboulsee 2011; Antony et al. 1995; Türkoğlu and Tüzün 2009), with limited scientific evidence to support these concerns, and multiple studies have found no association between ADEM incidence and seasonal influenza vaccines (Toplak et al. 2008; Baxter et al. 2016; Chen et al. 2018). Pellegrino et al. (2013) found that vaccines for seasonal influenza are the most frequently reported vaccines associated with ADEM onset. Currently, the only epidemiologically and pathologically proven association is with the Semple-type of the rabies vaccine (extracted from the neural tissue of rabies-infected adult sheep or goats and inactivated with phenol) (Hemachudha et al. 1987; Ubol et al. 1990), and limited data exists on the incidence of this condition following seasonal influenza vaccination.

The Advisory Committee on Immunisation Practices (ACIP) under the Centers for Disease Control and Prevention (CDC), which is governed by the United States (US) Department of Health and Human Service, updates their recommendations for influenza vaccines annually (Fiore et al. 2010). As per the 2010 recommendations, routine influenza vaccination is recommended for all individuals aged ≥ 6 months (Fiore et al. 2010).

Vaccine Adverse Event (AE) Reporting System database (VAERS) was created in 1990 (Shimabukuro et al. 2015; Varricchio et al. 2004) and co-administered by the CDC and the Food and Drug Administration (FDA) (Varricchio et al. 2004) to collect spontaneous reports of AEs following immunisation and manage vaccine safety (Shimabukuro et al. 2015). The main objectives of VAERS are to detect new, unusual, or rare vaccine AEs, assess the safety of newly approved vaccines and new recommendations for existing vaccines, identify potential risk factors, monitor the increase in known AEs, and determine and address possible reporting clusters (Shimabukuro et al. 2015; Varricchio et al. 2004). Spontaneous reporting systems (SRSs) have been used for pharmacovigilance assessments that reflect the realities of clinical practice (Hauben and Zhou 2003).

Pellegrino et al. (2015) estimated the incidence of ADEM following vaccination against H1N1 and seasonal influenza in the United States using vaccine coverage data from the CDC and cases from the VAERS. They estimated the incidence of ADEM occurring after seasonal influenza vaccines were administered and did not examine the risk for age or sex, as well as the difference in time-to-onset profiles depending on vaccine types (Pellegrino et al. 2013).

Here, we aimed to evaluate the relationship between the incidence of ADEM and seasonal influenza vaccines in a real-world setting using data from VAERS. Propensity score (PS) matching (PSM) (Ali et al. 2019; Jackson et al. 2017) was used to remove as many selection biases as possible, and disproportionality analysis was performed by calculating the adjusted reporting odds ratio (ROR) of reported ADEM cases associated with seasonal influenza vaccines using multiple logistic regression (Lee et al. 2020; Suzuki et al. 2015; van Puijenbroek et al. 2000; Fujimori et al. 2021). Furthermore, analysis of time-to-onset data has been proposed as a method to detect signals for AEs in SRSs (Sauzet et al. 2013). The data analysis of the VAERS database indicates the time-to-onset of AEs (Fujimori et al. 2021), and we aimed to analyse the time-to-onset of ADEM (Fujimori et al. 2021; Sauzet et al. 2013; Nakamura et al. 2015). Our results provide the clinical onset profile of ADEM associated with seasonal influenza vaccines.

2. Investigations and results

2.1. Selection of AE reports, AE cases, and ADEM and descriptive analysis

A single AE report may have more than two AEs. Therefore, we divided a single AE report into separate cases by the number of AEs. The VAERS database contains 390,352 reports from January 2011 to December 2020, including 127 ADEM cases (Table 1). A total of 1,869,140 cases were included in this study (Fig. 1). After excluding incomplete reports from patients under six months (0.5 years) of age and reports without sex or onset date information, there were 248,260 reports and 1,396,988 cases. A total of 343,824 seasonal influenza vaccines were administered during the study period (Fig. 1). Univariate analysis showed significant differences in the age group, sex, onset season, and age (years) between the seasonal influenza vaccine cases and other vaccine cases ($P < 0.001$) (Table 2).

Table 1: All vaccine types used when ADEM developed and number of ADEM from VAERS database between 2011 and 2020.

			Vaccine code	Vaccine type	number
			ADEN_4_7	ADENOVIRUS TYPE 4 & 7 VACCINE, LIVE ORAL	1
			DTAP	DIPHTHERIA AND TETANUS TOXOIDS AND ACELLULAR PERTUSSIS VACCINE	2
			DTAPIPV	DIPHTHERIA AND TETANUS TOXOIDS AND ACELLULAR PERTUSSIS VACCINE + INACTIVATED POLIOVIRUS VACCINE	5
			DTAPIPVHIB	DIPHTHERIA AND TETANUS TOXOIDS AND ACELLULAR PERTUSSIS VACCINE + INACTIVATED POLIOVIRUS VACCINE + HAEMOPHILUS B CONJUGATE VACCINE	1
TIV	Egg-based vaccine	IIV	FLU3	INFLUENZA VIRUS VACCINE, TRIVALENT	24
QIV	Egg-based vaccine	IIV	FLU4	INFLUENZA VIRUS VACCINE, QUADRIVALENT	17
QIV	Cell-based vaccine	IIV	FLUC4	INFLUENZA VIRUS VACCINE, QUADRIVALENT, CELL-CULTURE-DERIVED	5
TIV	Egg-based vaccine	LAIV	FLUN3	INFLUENZA VIRUS VACCINE (NASAL SPRAY)	2
QIV	Egg-based vaccine	LAIV	FLUN4	INFLUENZA VIRUS VACCINE QUADRIVALENT (NASAL SPRAY)	4
			FLUX	INFLUENZA VIRUS VACCINE, UNKNOWN MANUFACTURER	21
			FLUX(H1N1)	INFLUENZA (H1N1) MONOVALENT, UNKNOWN MANUFACTURER	1
			HEP	HEPATITIS B VIRUS VACCINE	3
			HEPA	HEPATITIS A	12
			HEPAB	HEPATITIS A + HEPATITIS B	1
			HIBV	HAEMOPHILUS B CONJUGATE VACCINE	2
			HPV4	HUMAN PAPILLOMAVAVIRUS QUADRIVALENT	6
			HPV9	HUMAN PAPILLOMAVIRUS 9-VALENT	6
			HPVX	HUMAN PAPILLOMAVIRUS (NO BRAND NAME)	1
			IPV	POLIOVIRUS VACCINE INACTIVATED	5
			MEN	MENINGOCOCCAL POLYSACCHARIDE VACCINE	6
			MENB	MENINGOCOCCAL GROUP B VACCINE, rDNA ABSORBED	1
			MMR	MEASLES, MUMPS AND RUBELLA VIRUS VACCINE, LIVE	11
			MMRV	MEASLES, MUMPS, RUBELLA AND VARICELLA VACCINE LIVE	5
			MNQ	MENINGOCOCCAL CONJUGATE VACCINE	6
			PNC	PNEUMOCOCCAL 7-VALENT CONJUGATE VACCINE	1
			PNC13	PNEUMOCOCCAL 13-VALENT CONJUGATE VACCINE	4
			PPV	PNEUMOCOCCAL VACCINE, POLYVALENT	3
			RAB	RABIES VIRUS VACCINE	2
			RVX	ROTAVIRUS (NO BRAND NAME)	1
			TDAP	TETANUS TOXOID, REDUCED DIPHTHERIA TOXOID AND ACELLULAR PERTUSSIS VACCINE, ADSORBED	19
			VARCEL	VARIVAX-VARICELLA VIRUS LIVE	8
			VARZOS	VARICELLA-ZOSTER VACCINE	6
			YF	YELLOW FEVER VACCINE	1

ADEM, acute disseminated encephalomyelitis; VAERS, Vaccine Adverse Event Reporting System.

TIV, trivalent influenza vaccine; QIV, quadrivalent influenza vaccine; Egg-based vaccine, egg culture-based influenza vaccine; Cell-based vaccine, cell culture-based influenza vaccine; IIV, inactivated influenza vaccine; LAIV, live-attenuated influenza vaccine.

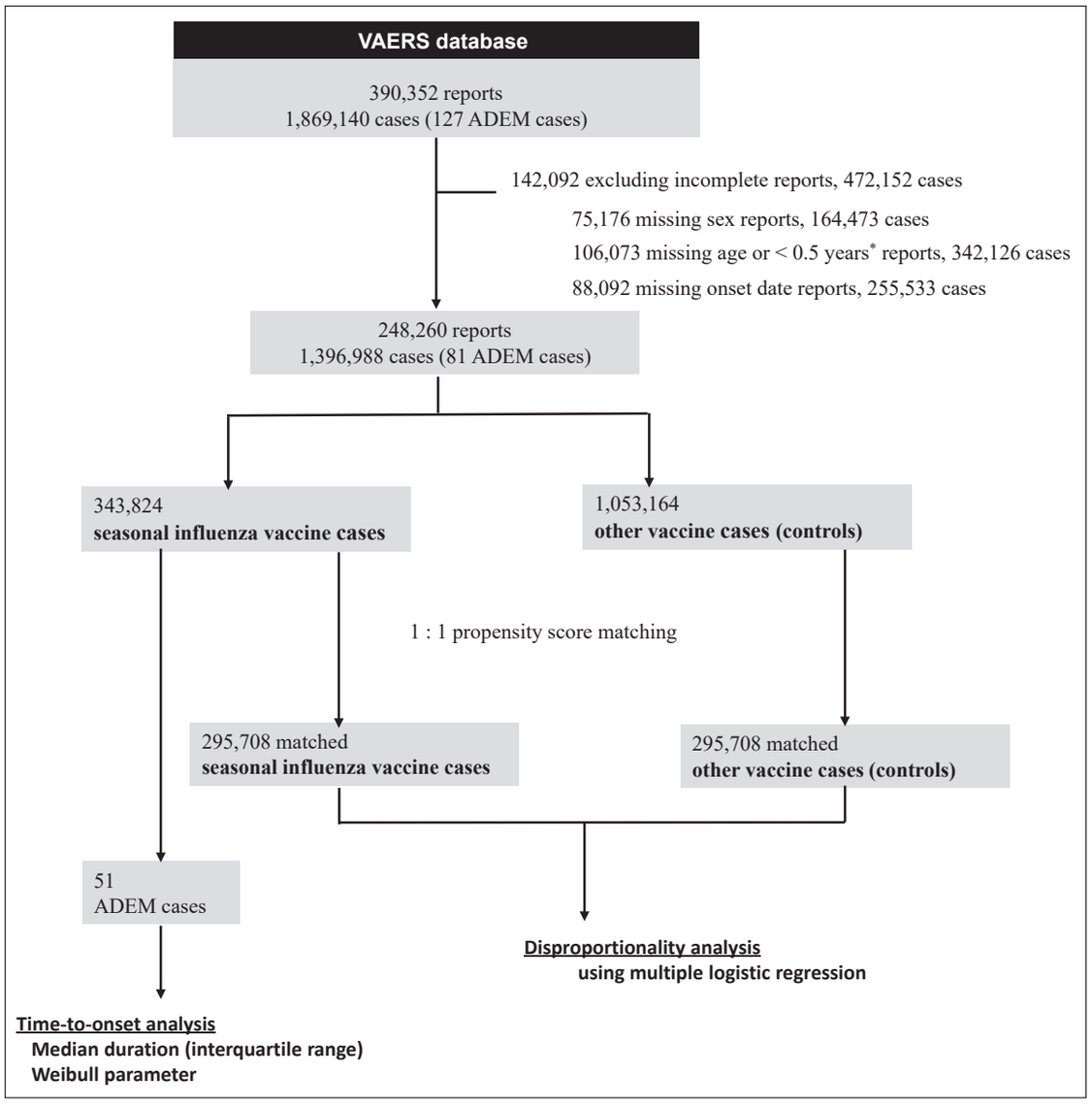

Fig. 1: Selection of cases for disproportionality analysis from the VAERS database between 2011 and 2020.
VAERS, Vaccine Adverse Event Reporting System; ADEM, acute disseminated encephalomyelitis. *Age ≥ 0.5 years was the recommended age for seasonal influenza vaccines in the United States.

Table 2: Characteristics of seasonal influenza vaccine cases and other vaccine cases before and after propensity score matching from VAERS database between 2011 and 2020.

		Before propensity score matching				After propensity score matching			
		n (%)		*P*-value†	SD	n (%)		*P*-value†	SD
Characteristics		Seasonal influenza vaccine cases	Other vaccine cases			Seasonal influenza vaccine cases	Other vaccine cases		
Total		343,824	1,053,164			295,708	295,708		
Age group n (%)	0.5–17 years	60,533 (17.6)	432,120 (41.0)	< 0.001	0.533	60,533 (20.5)	60,533 (20.5)	0.485	0.003
	18–64 years	185,822 (54.0)	415,446 (39.4)			145,188 (49.1)	144,787 (49.0)		
	≥ 65 years	97,469 (28.3)	205,598 (19.5)			89,987 (30.4)	90,388 (30.6)		
Sex n (%)	Female	240,235 (69.9)	669,278 (63.5)	< 0.001	0.134	204,304 (69.1)	202,127 (68.4)	< 0.001	0.016
	Male	103,589 (30.1)	383,886 (36.5)			91,404 (30.9)	93,581 (31.6)		
Onset season n (%)	Spring	7,580 (2.2)	233,352 (22.2)	< 0.001	1.346	7,580 (2.6)	7,580 (2.6)	1.000	< 0.001
	Summer	13,157 (3.8)	299,158 (28.4)			13,157 (4.4)	13,157 (4.4)		
	Fall	272,028 (79.1)	283,652 (26.9)			223,912 (75.7)	223,912 (75.7)		
	Winter	51,059 (14.9)	237,002 (22.5)			51,059 (17.3)	51,059 (17.3)		
Age (years)		45.8 ± 23.9	33.6 ± 27.0	< 0.001	0.477	45.2 ± 24.9	45.3 ± 25.2	0.605	0.001

VAERS, Vaccine Adverse Event Reporting System; SD, standardised difference.

†The *P*-value was calculated using Fisher's exact test or $\chi 2$-test for categorical variables and a t-test for continuous variables.

Table 3: Propensity score matched groups disproportionality analysis using univariate and multiple logistic regression from VAERS database between 2011 and 2020.

	VAERS	Univariate		Multiple	
	Vaccine codes included	ROR (95% CI)	*P*-value	Adjusted[‡] ROR (95% CI)	*P*-value
Seasonal influenza vaccines		3.00 (1.70–5.28)	0.001	3.02 (1.72–5.33)	< 0.001
The number of influenza viruses included					
Trivalent influenza vaccine (TIV)	FLU3, FLUN3	2.53 (1.34–4.79)	0.004	3.35 (1.76–6.37)	< 0.001
Quadrivalent influenza vaccine (QIV)	FLU4, FLUC4, FLUN4	4.59 (2.39–8.79)	< 0.001	3.23 (1.65–6.33)	< 0.001
The type of culture					
Egg culture-based influenza vaccine (Egg-based vaccine)	FLU3, FLU4, FLUN3, FLUN4	2.93 (1.64–5.25)	< 0.001	2.91 (1.63–5.22)	< 0.001
Cell culture-based influenza vaccine (Cell-based vaccine)	FLUC4	13.40 (4.91–36.60)	< 0.001	10.40 (3.74–28.90)	< 0.001
The type of influenza virus					
Inactivated influenza vaccine (IIV)	FLU3, FLU4, FLUC4	3.00 (1.68–5.37)	< 0.001	3.15 (1.76–5.63)	< 0.001
Live-attenuated influenza vaccine (LAIV)	FLUN3, FLUN4	7.46 (2.73–20.40)	< 0.001	2.64 (0.95–7.34)	0.063
Age (years)		0.97 (0.96–0.98)	< 0.001	0.98 (0.95–1.01)	0.120
Age group					
0.5–17 (years)		5.99 (3.35–10.70)	< 0.001	3.14 (0.97–10.20)	0.057
18–64 (years) (as reference)		1.00		1.00	
≥ 65 (years)		0.80 (0.34–1.88)	0.614	1.29 (0.38–4.42)	0.683
Sex					
Female (as reference)		1.00		1.00	
Male		1.82 (1.11–2.98)	0.017	0.67 (0.34–1.32)	0.244
Onset season					
Spring		0.80 (0.11–5.82)	0.824	0.43 (0.06–3.17)	0.409
Summer		0.46 (0.06–3.35)	0.443	0.53 (0.07–3.83)	0.525
Fall (as reference)		1.00		1.00	
Winter		2.96 (1.78–4.92)	< 0.001	2.01 (1.20–3.37)	0.008
Interaction term; age (years)×sex					
Age (years)×sex (female) (as reference)		1.00		1.00	
Age (years)×sex (male)		1.03 (1.00–1.05)	0.020	1.02 (1.00–1.04)	0.022

VAERS, Vaccine Adverse Event Reporting System; ROR, reporting odds ratio; CI, confidence interval.

[‡]Adjusted according to age group, sex, onset season, and age (years)×sex.

Table 4: Time-to-onset analysis of ADEM associated with seasonal influenza vaccines from VAERS database between 2011 and 2020.

	VAERS	ADEM	Median duration		Scale parameter, α (95% CI)	Shape parameter, β (95% CI)
	Vaccine codes included	(number for analysis)	(interquartile range) (days)	*P*-value[§]		
Total		51 (44)	11.0 (5.0–33.0)		27.95 (19.84–39.38)	0.91 (0.73–1.14)
The number of influenza viruses included						
Trivalent influenza vaccine (TIV)	FLU3, FLUN3	23 (19)	9.0 (2.5–29.0)	0.141	21.86 (13.57–35.21)	1.00 (0.70–1.42)
Quadrivalent influenza vaccine (QIV)	FLU4, FLUC4, FLUN4	24 (22)	16.5 (6.0–38.7)		33.53 (21.28–52.85)	0.97 (0.71–1.33)
The type of culture						
Egg culture-based influenza vaccine (Egg-based vaccine)	FLU3, FLU4, FLUN3, FLUN4	42 (36)	10.0 (5.0–24.0)	< 0.001	20.53 (15.12–27.86)	1.13 (0.88–1.45)
Cell culture-based influenza vaccine (Cell-based vaccine)	FLUC4	5 (5)	91.0 (79.0–125.0)		102.85 (74.76–141.50)	2.87 (1.35–6.10)
The type of influenza virus						
Inactivated influenza vaccine (IIV)	FLU3, FLU4, FLUC4	42 (37)	14.5 (6.0–31.0)	0.691	28.25 (19.69–40.54)	0.95 (0.74–1.21)
Live-attenuated influenza vaccine (LAIV)	FLUN3, FLUN4	5 (4)	9.0 (3.0–35.0)		23.34 (9.90–55.03)	1.20 (0.53–2.75)
Age group						
0.5–17 (years)		26 (25)	11.0 (6.0–23.3)	0.399	18.42 (12.55–27.02)	1.08 (0.80–1.46)
18–64 (years)		18 (13)	10.0 (0.75–31.0)		34.35 (19.30–61.14)	1.00 (0.66–1.51)
≥ 65 (years)		7 (6)	51.0 (6.0–104.0)		67.27 (30.51–148.33)	1.06 (0.53–1.51)
Sex						
Female		28 (23)	9.0 (4.5–41.0)	0.992	32.63 (20.10–52.97)	0.65 (0.65–1.23)
Male		23 (21)	15.0 (6.0–23.0)		23.17 (14.52–36.97)	0.97 (0.71–1.32)

ADEM, acute disseminated encephalomyelitis; VAERS, Vaccine Adverse Event Reporting System; CI, confidence interval.

[§]The *P*-value was calculated using the Mann–Whitney U test or Kruskal–Wallis test with the Bonferroni correction to analyse the medians of the time-to-onset data.

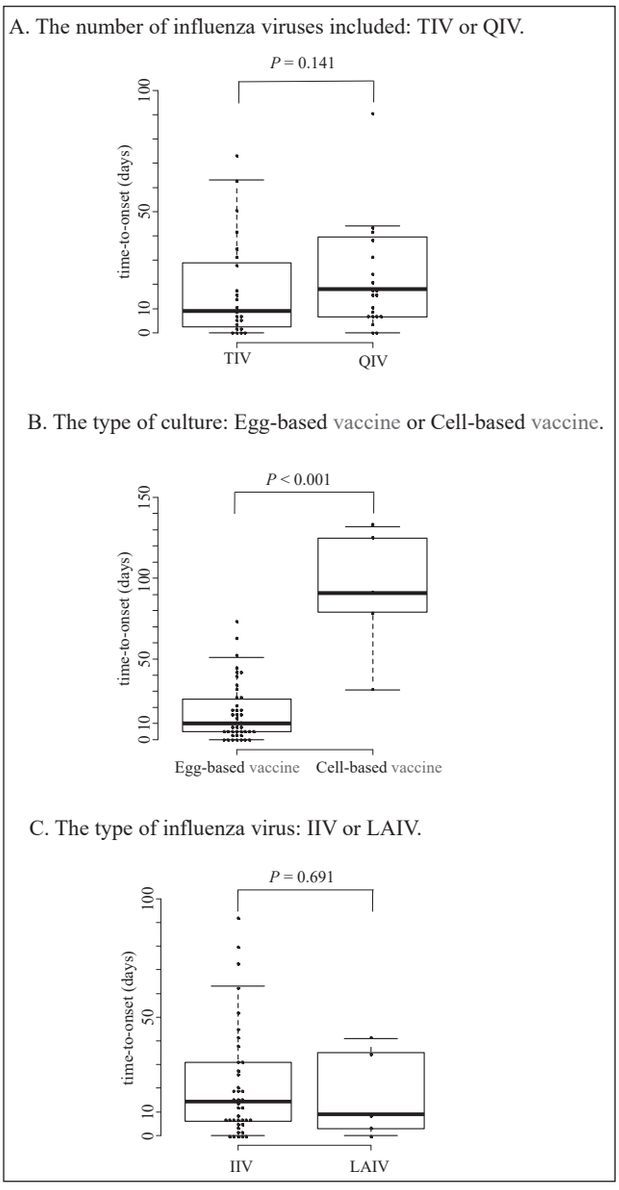

Fig. 2: Box plot of time-to-onset of ADEM associated with seasonal influenza vaccines.
ADEM, acute disseminated encephalomyelitis; TIV, trivalent influenza vaccine; QIV, quadrivalent influenza vaccine; Egg-based vaccine, egg culture-based influenza vaccine; Cell-based vaccine, cell culture-based influenza vaccine; IIV, inactivated influenza vaccine; LAIV, live-attenuated influenza vaccine.

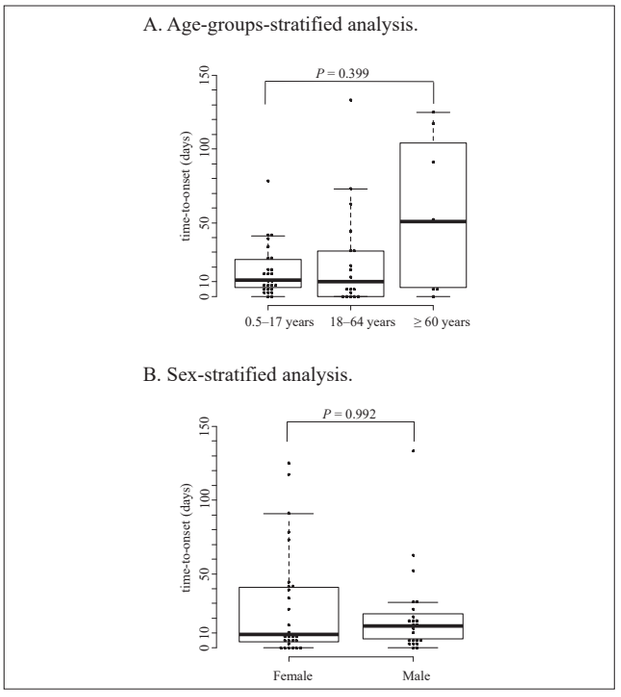

Fig. 3: Box plot of time-to-onset of ADEM associated with seasonal influenza vaccines based on age-stratified and sex-stratified analyses. ADEM, acute disseminated encephalomyelitis.

2.2. PSM and disproportionality analysis by multiple logistic regression

After PSM in a 1:1 ratio was used to remove as many selection biases as possible, the number of seasonal influenza vaccine cases and other vaccine cases were 295,708 (Fig. 1, Table 2). The changes in the number of seasonal influenza vaccine cases are shown in Fig. 1. The balance of variables before and after PSM is presented in Table 2. The standardised difference (SD) values of all variables after matching were < 0.1, which is close to randomisation.

We performed a multiple logistic regression analysis to partially adjust for confounding factors. The results of adjusted ROR after PSM are summarised in Table 3. The adjusted ROR for reporting ADEM incidence following seasonal influenza vaccines in the VAERS database was 3.02 (95% confidence interval [CI], 1.72–5.33). The adjusted RORs (95% CI) of the trivalent inactivated influenza vaccine (TIV), quadrivalent inactivated influenza vaccine (QIV), egg culture-based influenza vaccine (Egg-based vaccine), cell culture-based influenza vaccine (Cell-based vaccine), inactivated influenza vaccine (IIV), and live-attenuated influenza vaccine (LAIV) were 3.35 (1.76–6.37), 3.23 (1.65–6.33), 2.91 (1.63–5.22), 10.40 (3.74–28.90), 3.15 (1.76–5.63), and 2.64 (0.95–7.34), respectively (Table 3). In the type of vaccine, no signal was detected with LAIV alone. In the subgroup analysis, with the 18- to 64-year-old group and sex (female) as the reference group, the adjusted RORs of the 0.5- to 17-year-old and ≥ 65-year-old groups, sex (male), and age (years) × sex (male), were 3.14 (0.97–10.20), 1.29 (0.38–4.42), 0.67 (0.34–1.32), and 1.02 (1.00–1.04), respectively (Table 3). Regarding seasonality, with fall as the reference group, the adjusted RORs of spring, summer, and winter were 0.43 (0.06–3.17), 0.53 (0.07–3.83), and 2.01 (1.20–3.37), respectively (Table 3). The risk factor of ADEM following seasonal influenza vaccination was not age group or sex (male). In the onset seasons, a signal was detected only in winter.

2.3. Time-to-onset analysis

The time-to-onset profiles are presented in Table 4. The median duration (interquartile range) of ADEM following seasonal influenza vaccination (n = 51) was 11.0 (5.0–33.0) days. Regarding ADEM cases caused by TIV (n = 23) and QIV (n = 24), the durations were 9.0 (2.5–29.0) and 16.5 (6.0–38.7) days, respectively ($P = 0.141$) (Table 4, Fig. 2A). The ADEM cases associated with the administration of Egg-based (n = 42) and Cell-based (n = 5) vaccines had a median duration of 10.0 (5.0–24.0) and 91.0 (79.0–125.0) days, respectively ($P < 0.001$) (Table 4, Fig. 2B); the ADEM cases caused by IIV (n = 42) and LAIV (n = 5) had a median duration of 14.5 (6.0–31.0) and 9.0 (3.0–35.0) days, respectively ($P = 0.691$) (Table 4, Fig. 2C). The difference was statistically significant only in the type of culture. The Weibull shape parameter (WSP) β (95% CI) of ADEM for seasonal influenza vaccines was 0.91 (0.73–1.14) (Table 4). Only Cell-based vaccines had $\beta > 1$ (2.87 [1.35–6.10]) and was a wear-out failure type (Table 4). In addition, the scale parameter α of Egg-based and Cell-based vaccines was 20.53 (15.12–27.86) and 102.85 (74.76–141.50), respectively (Table 4), which was statistically

significant. The ADEM percentages within 30 days following vaccination with Egg-based and Cell-based vaccines were 78.6% (33/42 cases) and 0.0% (0/5 cases), respectively. ADEM developed within one month following vaccination with Egg-based. We further analysed ADEM in terms of the different age groups (0.5–17-year-old, 18–64-year-old, and ≥ 65-year-old groups) and sex. The median duration (interquartile range) of ADEM in the 0.5–17-year-old, 18–64-year-old, and ≥ 65-year-old groups were 11.0 (6.0 –23.3), 10.0 (0.75–31.0), and 51.0 (6.0–104.0) days, respectively (P = 0.399) (Table 4, Fig. 3A). Kruskal-Wallis test with the Bonferroni correction did not demonstrate any significant differences for the age groups. Although it was not significant, the highest median duration was in the ≥ 65-year-old age group. The median duration (interquartile range) of ADEM in females and males was 9.0 (4.5–41.0) and 15.0 (6.0–23.0) days, respectively (P = 0.992) (Table 4, Fig. 3B), which was not significant.

3. Discussion

The time-to-onset of ADEM depends on the type of vaccine, and ADEM developed after two months following vaccination with Cell-based vaccines, whereas it developed within one month following vaccination (Huynh et al. 2008; Shoamanesh and Traboulsee 2011; Antony et al. 1995; Türkoğlu and Tüzün 2009; Pellegrino et al. 2013) with Egg-based vaccines, according to the SRS database.

We acknowledge that it is difficult to draw general conclusions from subgroups with cases less than 10% of total sample size and that there may be some bias owing to the imbalance in the number of cases (n = 5 for Cell-based vs n = 42 for Egg-based vaccines). Nevertheless, our results have clinical relevance as they were deemed statistically significant. We could not find any reliable literature on the cause. Although it is possible that the cause may be allergic, we believe that this is unlikely, considering the rigor of safety assessment before vaccines enter clinical trials.

Cell-based vaccines had a safety profile similar to that of Egg-based vaccines (Nolan et al. 2016). To the best of our knowledge, this is the first study comparing the time-to-onset of individual AEs for Egg-based and Cell-based vaccines and reporting the differences. In a randomised controlled trial of Cell-based inactivated and Egg-based live attenuated influenza vaccines in children and young adults to 2019–2020, compared to Egg-based vaccines, Cell-based vaccines were revealed to induce a significantly higher antibody response (Williams et al. 2022). However, the relationship with the longer time-to-onset of ADEM is unclear. The mechanism of ADEM development is poorly understood; to elucidate the mechanism underlying the longer ADEM time-to-onset following Cell-based vaccination than that of Egg-based vaccination, further studies are required. Longer ADEM time-to-onset following Cell-based vaccination may also be why the time-to-onset was longer in the ≥ 65-year-old group than in other age groups. In the ≥ 65-year-old group, the reported rate of ADEM following Cell-based vaccination was higher than that in the other age groups (data not shown). This finding based on actual clinical data is important for clinicians; therefore, this study provides a detailed profile.

Though the breadth of antibody responses in infection versus vaccination is quite different (Miyauchi et al. 2021), post-vaccination and post-infection ADEM may have a common pathogenic mechanism (Shoamanesh and Traboulsee 2011). A molecular mimicry theory (Tenembaum et al. 2007; Stüve and Zamvil 1999; Bennetto and Scolding 2004; Huynh et al. 2008) has been proposed for the pathogenesis of ADEM. Given that vaccines work by priming the immune system, it is biologically plausible that immunisation may be associated with subsequent ADEM. Antigenic epitopes are shared between an inoculated vaccine and host CNS proteins. At the inoculation site, the pathogen is initially processed by T-cell activation and cross-activation of antigen-specific B cells. These autoreactive cells can enter the CNS during immune surveillance and may encounter homologous myelin proteins. Although establishing the relative primacy of humoral and cellular immune responses may be difficult, these reactions may be responsible for generating CNS inflammatory damage in ADEM (Tenembaum et al. 2007; Stüve and Zamvil 1999; Bennetto and Scolding 2004; Huynh et al. 2008).

In the disproportionality analysis after PSM, the ROR signal for ADEM with seasonal influenza vaccination was detected (adjusted ROR, 3.02; 95% CIs 1.72–5.33). Although the association between influenza vaccination and ADEM incidence is still controversial (Huynh et al. 2008; Shoamanesh and Traboulsee 2011; Antony et al. 1995; Türkoğlu and Tüzün 2009; Toplak et al. 2008; Baxter et al. 2016; Chen et al. 2018), we need to closely monitor and manage ADEM events after seasonal influenza vaccination. In this study, no signal was detected with LAIV alone. LAIV stimulates both mucosal and systemic immune responses compared with the inactivated influenza vaccine (McNeela and Mills 2001). Although similar results have been reported for Guillain–Barré syndrome (GBS) following seasonal influenza vaccination (Fujimori et al. 2021), the reason behind this contradiction is unknown. The ROR is an indicator of an increased risk of AE reporting; however, it does not indicate the risk of AE occurrence in absolute terms (Montastruc et al. 2011); therefore, the results of this study should be interpreted with caution.

Previous studies have reported that the development of ADEM after seasonal influenza vaccination is not restricted to a specific age (Bennetto and Scolding 2004; Pellegrino et al. 2013) and we obtained the same result in our study. Following seasonal influenza vaccination, females typically develop higher antibody responses (Voigt et al. 2019; Engler et al. 2008) and report more AEs of vaccination (Engler et al. 2008; Beyer et al. 1996) than males. As the immune system probably evolves differently with age in males and females, their response to vaccines may differ (Tadount et al. 2020). Pellegrino et al. reported that the incidence of post-vaccination ADEM, which is not limited to only seasonal influenza vaccines, depicted a male predominance, with a female/male ratio of 0.66 (Pellegrino et al. 2013) obtained from the VAERS database. Our results differ from these results. However, we also detected a signal in males in the univariate logistic regression analysis. Pellegrino et al. (2013) also reported that they had corrected for the presence of female patients with ADEM following sex-specific vaccination against the human papillomavirus. It is possible that they obtained male-dominated results because of insufficient coordination. Therefore, the monitoring for ADEM after seasonal influenza vaccination should be performed regardless of age or sex.

At the time of influenza A (H1N1) 2009 monovalent vaccination, the most comprehensive safety surveillance agenda in the US to date was implemented. This data analysis of approximately 23 million vaccinated people from six AE-monitoring systems is believed to have obtained almost all GBS cases, and no seasonality of GBS was observed (Salmon et al. 2013). The seasonality of our study signal may be because of the use of SRS data. Although ADEM seasonality signal was observed in our study, we believe that no seasonality signal will be observed if all ADEM cases are obtained, as observed with GBS cases (Salmon et al. 2013) in the previous study.

Our study had some limitations. First, the SRSs, such as the VAERS database, are subject to under-reporting, over-reporting, missing data, bias, confounding factors, lack of a control population as a reference group, lack of adequate data quality, and the possible existence of reports based on indirect information, such as those heard on TV or read in newspapers. ROR computation does not allow the quantification of the risk of an AE but only suggests a possible causal relationship between a vaccine and an AE (Montastruc et al. 2011). Second, we cannot exclude the possibility condition due to unadjusted confounding factors, such as exposure to previous infections (Mosterín Höpping et al. 2016; Jackson et al. 2010) or the intervention of regulatory authorities, which may influence the VAERS database information based on the year of reporting (Lee et al. 2020). Third, the sample size of the study after PSM decreased from 1,396,988 to 591,416, and the loss of data of several cases may have led to selective bias. Fourth, this study focused solely on the risk of ADEM following seasonal influenza vaccination and did not address the benefits of the vaccination.

Despite the limitations inherent to SRS, our findings highlighted the importance of characterisation of the safety profile of seasonal influenza vaccines. We demonstrated the potential risk of ADEM associated with seasonal influenza vaccines based on a disproportionality analysis. Our results regarding ADEM development following vaccination with Egg-based vaccines were corroborated by previous studies (Huynh et al. 2008; Shoamanesh and Traboulsee 2011; Antony et al. 1995; Türkoğlu and Tüzün 2009; Pellegrino et al. 2013).

With the knowledge of timing and outcome profiles, such as ROR and time-to-onset of ADEM that actually occurs in clinical practice based on real-world data, early intervention by neurologists and general practitioners would be possible, thus reducing the risk of overlooking ADEM. By analysing the time-to-onset, we found that ADEM in Egg-based vaccinated patients developed within a month and after two months in Cell-based vaccinated patients. Patients vaccinated with seasonal influenza vaccines should be closely monitored during the onset period for the initial symptoms of ADEM, namely fever, malaise, myalgia, headache, and vomiting. Although our results were not comprehensive, they remain valuable as they support the results of existing clinical studies (Pellegrino et al. 2015). We believe that our results represent a valuable contribution to clinical knowledge and may assist in ADEM management.

4. Experimental

4.1. Data sources

Data were retrieved from the VAERS database. Anyone can report an AE to VAERS, including healthcare professionals, vaccine manufacturers, patients, parents and caregivers, and others. Reports are submitted voluntarily, either directly from individual reporters, who may be reporting for themselves or others, or secondarily from vaccine manufacturers that also receive spontaneous reports and, in turn, submit them to VAERS (Shimabukuro et al. 2015; Varricchio et al. 2004). All reports were approved without discerning clinical causality (Shimabukuro et al. 2015). Data from the primary reports, with sensitive patient information removed, are publicly available on the VAERS website (www.vaers.hhs.gov/data/index) as an online downloadable dataset (Shimabukuro et al. 2015). To protect patient privacy, additional information obtained during follow-up on individual VAERS reports was not included in the publicly available data (Shimabukuro et al. 2015). In this study, we obtained AE reports, which were limited to those reported by the US population from January 2011 to December 2020.

In the VAERS database, the AE data of each case are present in three sets of files: VAERSDATA.CSV, VAERSVAX.CSV, and VAERSSYMPTOMS.CSV (CDC and FDA 2020). We constructed a relational database that integrated them using Microsoft Access® Office 365 (Microsoft Corporation, Redmond, WA, USA) with VAERS_ID as a key code. Symptoms were coded using preferred terms (PTs) in the Medical Dictionary for Regulatory Activities (MedDRA), which is a collection of international medical terminology prepared by the International Council for Harmonisation to standardise and unify AE reports (ICH 2021).

4.2. Selection of AE reports, AE cases, and ADEM and descriptive analysis

Seasonal influenza vaccine AE reports were defined as those filed with text that included the word 'FLU' and excluded those with (H1N1) in the vaccine code.

To compare conventional vaccines (such as inactivated, trivalent, and egg culture-based vaccines) and other vaccines (such as live-attenuated, quadrivalent, and cell culture-based vaccine), seasonal influenza vaccines were classified based on the following criteria: (1) the number of influenza viruses included: trivalent or quadrivalent; (2) the type of culture: egg based or non-egg based (cell-cultured); and (3) the type of influenza virus: live-attenuated or inactivated (Lee et al. 2020).

AEs were retrieved using the following PTs: 'acute disseminated encephalomyelitis' (PT code: 10000709) (ICH 2021).

To compare the baseline characteristics of seasonal influenza vaccine cases and other vaccine cases, the *P*-value was calculated using Fisher's exact test or χ^2-test for categorical variables and a t-test for continuous variables. Statistical significance was set at $P < 0.05$.

4.3. PSM and disproportionality analysis by multiple logistic regression

We evaluated the association between seasonal influenza vaccines and ADEM and the risk factors associated with ADEM following seasonal influenza vaccination using disproportionality analysis (Poluzzi et al. 2010; Montastruc et al. 2011). In disproportionality analysis, several point estimates such as the ROR and the proportional reporting ratio have been used to detect signals in spontaneously reported data (Poluzzi et al. 2010; Montastruc et al. 2011). In this study, we applied the ROR, which is defined as the ratio of the odds of reporting an AE versus all other events associated with seasonal influenza vaccines, compared with the reporting odds for AEs associated with all other vaccines present in the database. The ROR was calculated using a two-by-two contingency table (van Puijenbroek et al. 2002) to detect potential associations between seasonal influenza vaccines and ADEM and was expressed as point estimates with 95% CIs. The detection of a signal is dependent on signal indices exceeding a predefined threshold. Safety signals are considered significant when the ROR estimates and the lower limits of the corresponding 95% CI exceed 1(van Puijenbroek et al. 2002). Two or more cases (van Puijenbroek et al. 2002; Poluzzi et al. 2012) were required to define a signal.

Table 5: Association between inoculation against seasonal influenza or other and sex.

Inoculation against seasonal influenza or other		Coefficient[‖]	Standard error	P-value
All	Age (years)	0.016	< 0.001	< 0.001
	Sex (male) (reference female)	−0.253	0.008	< 0.001
	Age (years)×sex (male) (reference female)	0.004	< 0.001	< 0.001
Male	Age (years)	0.020	< 0.001	< 0.001
Female	Age (years)	0.016	< 0.001	< 0.001

[‖]Coefficient: logistic regression coefficient.

The interaction analyses were conducted to determine the influence of the interactions between age (years) and sex, considering the effect of age on the relationship between inoculation against seasonal influenza or other diseases and sex, which was significant ($P < 0.001$) (Table 5). This analysis was performed as previously described (Fukuhara et al. 2021; Jia et al. 2019). To remove as many selection biases as possible, we applied PSM. The PS for seasonal influenza vaccine exposure was estimated by a logistic regression model with the following four variables as predictors: age group (0.5–17-, 18–64-, and ≥ 65-year-old groups) (Pellegrino et al. 2013), sex (female and male), onset season (spring, summer, fall, and winter) (Lee et al. 2020), and the interaction term between age (years) and sex. The onset seasons were defined as spring including March, April, and May; summer including June, July, and August; fall including September, October, and November; winter including December, January, and February. Each case that received the seasonal influenza vaccine was matched to a case that received another vaccine on the PS by using the greedy nearest neighbour matching without replacement within a calliper. The calliper value was defined as '0.05 × the standard deviation of the logit transformation-applied PS estimate'. The SD was calculated to evaluate the balance of variables of the matched data (Ali et al. 2019). An SD value of < 0.1 (Ali et al. 2019; Jackson et al. 2017) was considered as balanced. Using the PS estimates and the calliper value, the seasonal influenza vaccine case group and the other vaccine case group were matched. The selection of cases for the disproportionality analysis is shown in Fig. 1.

To evaluate the relationship between seasonal influenza vaccines and ADEM and the risk factors of ADEM development using matched data, univariate and multiple logistic regression analyses were performed. We performed a multiple logistic regression analysis to partially adjust for confounding factors. Acute disseminated encephalomyelitis was considered as the objective variable, while the patient characteristics (age group, sex, and onset season), the interaction term between age (years) and sex, and the classification of seasonal influenza vaccines (Lee et al. 2020; Jia et al. 2019) were considered as the explanatory variables. Subgroup analysis was performed by stratifying the groups according to age: 0.5–17, 18–64, and ≥ 65 years (Pellegrino et al. 2013), sex, or onset season. One patient characteristic (age group, sex, or onset season) was considered as the objective variable, while the other patient characteristics and the interaction term between age (years) and sex were considered as the explanatory variables.

4.4. Time-to-onset analysis

Time-to-onset from the VAERS database was determined as the time from the vaccination date to the date of AEs occurrence. We excluded reports that lacked complete AE occurrences and vaccination dates. The median duration, quartile, and WSP tests were used to evaluate the time-to-onset data (Fujimori et al. 2021; Sauzet et al. 2013; Nakamura et al. 2015). The WSP test, which describes the non-constant rate of AEs incidence (i.e., the risk of increase or decrease over time) in SRSs, was used to statistically analyse the time-to-onset data (Fujimori et al. 2021; Sauzet et al. 2013; Nakamura et al. 2015). The scale parameter α determines the scale of the distribution function, while the shape parameter β determines the shape of the distribution function. A larger α value shows stretched distribution, whereas a smaller α value indicates shrinkage. The larger the α value, the more the distribution shifts to the right, and the lower the height. The hazard function for the Weibull model increases over time if $\beta > 1$ (wear-out failure type), decreases if $\beta < 1$ (initial failure type), and if $\beta = 1$, where it is constant over time (random failure type) (Sauzet et al. 2013). Subgroup analysis was further performed by stratifying the groups according to age or sex. We calculated the *P*-value using the Mann-Whitney U test or Kruskal-Wallis test with the Bonferroni correction to analyse the median duration of the time-to-onset data. Statistical significance was set at $P < 0.05$.

Statistical analyses were performed using EZR (Easy R) version 1.54 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) (Kanda 2013). Time-to-onset analysis using the WSPs was performed with R version 3.6.3 (The R Foundation for Statistical Computing, Vienna, Austria).

4.5. Ethics approval and consent to participate

Ethical approval was not sought because the study involved only analysis of data obtained from a public database.

Conflicts of interest: none declared.

Informed consent to participate: not applicable.

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