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Multiregional Population-Based Cohort Study for Evaluation of the Association Between Herpes Zoster and mRNA Vaccinations for Severe Acute Respiratory Syndrome Coronavirus-2: The VENUS Study

Chieko Ishiguro,[1] Wataru Mimura,[1] Yukari Uemura,[2] Megumi Maeda,[3] Fumiko Murata,[3] and Haruhisa Fukuda[3]

[1]Section of Clinical Epidemiology, Department of Data Science, Center for Clinical Sciences, National Center for Global Health and Medicine, Tokyo, Japan, [2]Section of Biostatistics, Department of Data Science, Center for Clinical Sciences, National Center for Global Health and Medicine, Tokyo, Japan, and [3]Department of Health Care Administration and Management, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan

Background. This study was performed to assess the increased risk of herpes zoster (HZ) associated with mRNA vaccines for coronavirus disease 2019.

Methods. This population-based cohort study was conducted in 4 municipalities in Japan. Individuals covered under public health insurance systems without a history of HZ were followed from October 1, 2020 to November 30, 2021. Incidence rates of HZ within 28 days of BNT162b2 or mRNA-1273 vaccination were compared. Adjusted incidence rate ratios (IRR) and 95% confidence intervals (CI) were estimated using a Poisson regression model, including vaccination status as a time-dependent covariate. Subgroup analyses by sex, age, and municipality were also conducted.

Results. A total of 339 548 individuals (median age, 74 years) were identified. During follow up, 296 242 individuals (87.2%) completed the primary series, among whom 289 213 and 7019 individuals received homologous BNT162b2 and mRNA-1273 vaccines, respectively. The adjusted IRRs of the first and second BNT162b2 vaccinations were 1.05 (95% CI, 0.84–1.32) and 1.09 (95% CI, 0.90–1.32), respectively. No cases of HZ were observed after mRNA-1273 vaccination. In subgroup analysis, the adjusted IRR of the second BNT162b2 vaccination was 2.94 (95% CI, 1.41–6.13) in individuals aged <50 years old.

Conclusions. No increased risk of HZ was found after BNT162b2 vaccination in the overall study population. However, an increased risk was observed in the younger subgroup.

Keywords. adverse reaction; COVID-19; herpes zoster; Japan; mRNA vaccine.

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, has affected people's lives worldwide. The BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna/Takeda) vaccines received the Food and Drug Administration's Emergency Use Authorization in December, and vaccination started worldwide soon after. In Japan, vaccinations with BNT162b2, mRNA-1273, and ChAdOx1-S (AstraZeneca) began in February, May, and August 2021, respectively. In November 2021, 9 months after vaccination began, 95.6 million people (approximately 75% of the national population) had received 2 doses of mRNA vaccine, 99.9% of which were BNT162b2 or mRNA-1273 vaccine [1].

Recently, safety concerns have been raised regarding the causality between mRNA vaccines for COVID-19 and the occurrence of herpes zoster (HZ), which is an acute viral infection that occurs after the reactivation of the varicella-zoster virus (VZV). This safety concern was not identified at the time of approval [2, 3]; however, many spontaneous case reports of HZ after COVID-19 vaccination have been published worldwide [4]. In addition, safety signals of HZ after COVID-19 vaccination have arisen from data mining of individual safety case report databases [5, 6]. Furthermore, increased risk was found in active monitoring for adverse events of special interest (AESI) of mRNA vaccines using large healthcare database in Israel [7].

In response to this situation, observational studies specific to this clinical question have been conducted in several countries; however, the increased risk of HZ due to COVID-19 vaccines remains controversial. No increased risk was found in studies in the United States and Israel [8, 9], whereas a study conducted

in Hong Kong [10] identified an increased risk of HZ after COVID-19 vaccination, and studies using multicountry data suggested both an increased risk and no increased risk [11, 12]. In Japan, HZ has been on the list of COVID-19 vaccines' AESI created by the National Council for Pharmacovigilance of postauthorization vaccines since November 2021 [13]; however, the monitoring of HZ has been based on individual case safety reports, and there is no information on population-based studies in Japan. Therefore, this study aimed to assess whether the frequency of HZ increases after mRNA vaccination for COVID-19 using a large population-based cohort study.

METHODS

Data Source

We used Vaccine Effectiveness, Networking, and Universal Safety (VENUS) Study data from 4 municipalities in Japan (1 Chubu, 1 Chugoku, and 2 Kanto regions). The VENUS Study is a municipality-based database that includes data from 2 public health insurers' claims: the National Health Insurance System, which covers persons aged ≤74 years who are self-employed, parttime employed, retired, or working in the agriculture, forestry, and fishery industries, and the Latter-Stage Older Persons Health Care System, which covers persons aged ≥75 years and those aged 65–74 years with specific disabilities. The data contained information on outpatient clinic visits and hospital admissions, including enrollees' age, sex, diagnoses, medical examinations, and treatments. Diagnoses were established based on the *International Classification of Diseases, Tenth Revision* (ICD-10) codes, and medications were established using the national code for claims data [14, 15]. The vaccination record system (VRS) includes information on the types of vaccines administered and vaccination dates. The SARS-CoV-2 infection registry (the Health Center Real-time Information-sharing System on COVID-19 [HER-SYS]) includes information on positive SARS-CoV-2 test results and date of specimen collection. The claims data were linked to the VRS and HER-SYS data at the individual level by anonymous residential identifiers [16].

Study Cohort

We conducted a population-based cohort study to assess the incidence of first-time HZ. We included residents aged >11 years on October 1, 2020 (cohort entry date [CED]). Residents who had a previous SARS-CoV-2 infection, history of HZ before CED, and less than 1 year of insurance enrollment before CED were excluded. The follow-up period was from CED until the earliest date of the following: occurrence date of HZ; November 30, 2021; date of death; the day before the sample collection date for the SARS-CoV-2 test with a positive result; the day before vaccination with ChAdOx1-S. The study design diagram is shown in Supplementary Figure 1.

Definition of Vaccination Status, Outcome, and Covariate

The vaccination status of each individual was categorized according to vaccine type (BNT162b2 or mRNA-1273) and dose: unvaccinated, within 28 days of the first dose (or from the first vaccination date until the second vaccination date), after day 29 of the first vaccination until the second vaccination (ie, people who did not receive the second dose as scheduled), within 28 days of the second dose, and after day 29 of the second dose. Illustrations of the definition of vaccination status are shown in Supplementary Figure 2. The onset of HZ in inpatient and outpatient settings was defined as the prescription of antiviral drugs with an indication for HZ (acyclovir, valacyclovir, famciclovir, vidarabine, and amenamevir) at the same time as the diagnosis of HZ (ICD-10 code B02). We obtained background information of the individuals to account for confounding factors: age at CED, sex, city, and number of clinic/hospital visits during the year before their CED as an indicator of healthcare-seeking behavior. In addition, underlying comorbidities and medicine use suggested as potential risk factors for HZ [17, 18] were identified within the year before their CED: rheumatic disease, kidney disease, liver disease, diabetes, cancer, human immunodeficiency virus/acquired immune deficiency syndrome (AIDS), organ transplant, systemic corticosteroids, and immunosuppressants. Supplementary Table 1 provides a detailed definition of the covariates. All code lists were checked for appropriateness by at least 2 or more healthcare professionals (physicians or pharmacists).

Statistical Analysis

We described the baseline characteristics of the individuals in the cohort. We also tabulated the baseline characteristics of the unvaccinated and risk periods. In the primary analysis, the incidence rate of HZ within 28 days of each dose was compared with that during the unvaccinated period. Poisson regression models were used to estimate the crude and adjusted incidence rate ratios (IRRs) with 95% confidence intervals (CIs). Vaccination status was included in the model as a time-dependent covariate. For confounding adjustment, age (continuous variable), sex, municipality, clinic/hospital visit counts (continuous variable), comorbidities, and medication use were included in the model to estimate adjusted IRRs. Subgroup analyses according to age, sex, and municipality were also conducted. The age subgroups were defined as <50 years and ≥ 50 years. This is because shingles is known to be particularly prevalent in people aged ≥ 50 years in Japan, and the indication for the shingles vaccine in Japan is limited to people aged ≥ 50 years [18]. An additional analysis was performed in the full cohort using the model, including an interaction term between vaccination status and factors showing a trend of effect modification from the subgroup analysis, and *P* for effect modification was calculated. In the secondary analysis, we compared the incidence rate of HZ after 29 days of each dose with that in the

unvaccinated period and estimated the IRRs and 95% CIs. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Patient Consent Statement

This study was approved by the Kyushu University Institutional Review Board for Clinical Research (no. 2021-399). The requirement for individual informed consent was waived based on the Japanese ethical guidelines, because this secondary analysis used routinely collected anonymized data by the municipalities.

RESULTS

Study Population

Our population cohort included 339 548 individuals, yielding 377 428 person-years (1.1 years on average). Almost all individuals (328 992, 96.6%) were followed up until the end of the study period; 6830 (2.0%) residents died; 2048 (0.6%) were infected with SARS-CoV-2; and 38 (0.01%) received ChAdOx1-S vaccination during the study period. The baseline characteristics of the study cohort at CED and the number of vaccinations through the study period are presented in Supplementary Table 2. The median age was 74 years, and 57.8% of the patients were female. The median number of clinic/hospital visits was 16 (interquartile range [IQR], 9–27). During follow up, 296 242 individuals (87.2%) completed the primary immunization

(first and second doses), and 289 213 and 7019 individuals had homologous vaccinations of BNT162b2 and mRNA-1273, respectively. The median time between the administration of the first and second doses was 21 days (IQR, 21–21 days) for homologous BNT162b2 vaccination and 28 days (IQR, 28–28) for homologous mRNA-1273 vaccination. The risk time characteristics in each vaccination status are presented in Table 1.

Herpes Zoster Risk Analysis

Table 2 presents the results of the primary analyses. The number of patients with HZ onset in the unvaccinated group was 1128 (426/100 000 person-years). Within 28 days after the first and second doses of BNT162b2, 80 (476/100 000 person-years) and 112 individuals (479/100 000 person-years), respectively, had HZ onset. No cases of HZ onset were observed within 28 days of the first or second dose of mRNA-1273. The adjusted IRRs of the first and second BNT162b2 vaccinations were 1.05 (95% CI, 0.84–1.32) and 1.09 (95% CI, 0.90–1.32), respectively. Subgroup analysis by age showed an increased risk of HZ in those aged <50 years. In the subgroup analysis by sex or municipality, the results showed the same trend as that in the primary analysis (Table 3). In the results of the additional analysis with the model, including the interaction item between age and vaccination status, P for effect modification of the first and second vaccinations were .45 and >.01, respectively. In the secondary analysis, which was a comparison of HZ risk after day 29 of

Table 1. Characteristics of the Study Cohort in Each Vaccination Status druing the Follow-up Period[a]

Characteristic		Unvaccinated Period	BNT162b2 Vaccinated Period		mRNA-1273 Vaccinated Period	
			First Dose[b]	Second Dose[b]	First Dose[b]	Second Dose[b]
Total		264 858 (100)	16 811 (100)	22 535 (100)	599 (100)	536 (100)
Sex	Male	112 778 (42.6)	6979 (41.5)	9353 (41.5)	296 (49.4)	258 (48.2)
	Female	152 080 (57.4)	9832 (58.5)	13 182 (58.5)	303 (50.6)	277 (51.8)
Age	<50 years	39 404 (14.9)	1425 (8.5)	1756 (7.8)	245 (40.9)	234 (43.7)
	≥50 years	225 454 (85.1)	15 386 (91.5)	20 779 (92.2)	354 (59.1)	301 (56.3)
Number of clinic/hospital visits	<16	144 776 (54.7)	8386 (49.9)	11 171 (49.6)	460 (76.8)	416 (77.6)
	≥16	120 082 (45.3)	8424 (50.1)	11 364 (50.4)	139 (23.2)	120 (22.4)
Covariates	Rheumatic disease	9288 (3.5)	630 (3.7)	849 (3.8)	10.5 (1.8)	9.0 (1.7)
	Kidney disease	11 970 (4.5)	808 (4.8)	1083 (4.8)	8.6 (1.4)	7.6 (1.4)
	Liver disease	47 036 (17.8)	3226 (19.2)	4347 (19.3)	66.0 (11.0)	58.7 (11.0)
	Diabetes	21 446 (8.1)	1469 (8.7)	1979 (8.8)	27.1 (4.5)	22.5 (4.2)
	Cancer	31 837 (12.0)	2174 (12.9)	2936 (13)	36.1 (6.0)	30.8 (5.7)
	HIV/AIDS	132 (0.0)	7.6 (0.0)	10.1 (0.0)	0.6 (0.1)	0.5 (0.1)
	Organ transplant	104 (0.0)	6.5 (0.0)	8.7 (0.0)	0.2 (0.0)	0.2 (0.0)
	Systemic corticosteroids	45 103 (17.0)	2973 (17.7)	3994 (17.7)	88.1 (14.7)	77.8 (14.5)
	Immunosuppressants	1554 (0.6)	95.1 (0.6)	128 (0.6)	2.9 (0.5)	2.6 (0.5)
Municipality	City A	47 527 (17.9)	3240 (19.3)	4273 (19.0)	16.1 (2.7)	9.5 (1.8)
	City B	57 547 (21.7)	3434 (20.4)	4580 (20.3)	240 (40.0)	243 (45.4)
	City C	72 088 (27.2)	4486 (26.7)	6063 (26.9)	186 (31.1)	131 (24.4)
	City D	87 696 (33.1)	5650 (33.6)	7619 (33.8)	157 (26.2)	152 (28.4)

Abbreviations: AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus.

[a]Data are presented as person-years (%).

[b]Within 28 days of vaccination.

Table 2. Incidence Rate Ratios of Herpes Zoster Within 28 Days of mRNA Vaccinations

Exposure	Number of Individuals	PY	Outcome	Incidence Rate/100 000 PY	Crude IRR[a] (95% CI)	Adjusted IRR[a,b] (95% CI)
Unvaccinated period	339 548	264 858	1128	426	Reference	Reference
BNT162b2						
Within 28 days after the first dose[c]	289 842	16 811	80	476	1.12 (0.89–1.40)	1.05 (0.84–1.32)
Within 28 days after the second dose	287 103	22 535	112	497	1.17 (0.96–1.42)	1.09 (0.90–1.32)
mRNA-1273						
Within 28 days after the first dose	7805	599	0	–	–	–
Within 28 days after the second dose[c]	6950	536	0	–	–	–

Abbreviations: PY, person-years; CI, confidence interval; IRR, incidence rate ratio.

[a]Estimated using Poisson regression model.

[b]Adjusted for age, sex, municipality, clinic or hospital visit count, rheumatic disease, kidney disease, liver disease, diabetes, cancer, acquired immune deficiency syndrome/human immunodeficiency virus, organ transplant, systemic corticosteroids, and immunosuppressants.

[c]When the second dose was administered within a 28-day interval of the first dose, the risk period ended on the day before the second dose was given.

each vaccination with that in the unvaccinated period, an increased risk was observed after day 29 of the first vaccination with BNT162b2 (Supplementary Table 3).

DISCUSSION

This multiregional population-based cohort study using VENUS Study data covering the population of the 4 municipalities in Japan assessed the increased risk of HZ associated with mRNA vaccination for COVID-19. In the primary analysis, no increased risk of HZ was observed within 28 days of BNT162b2 vaccination. Meanwhile, there were no HZ cases after mRNA-1273 vaccination. An effect-measure modification by age was found in the subgroup analysis, and an increased risk after day 29 of the first vaccination was found in the secondary analysis.

A recent study using a large population-based database in the United States, which is the only study that considers both HZ vaccinations and SARS-CoV-2 infection as confounders in addition to other characteristics, showed no increased risk after receiving both mRNA vaccines [8]. Adjustment of these factors is important because SARS-CoV-2 infection is believed to be a risk factor for HZ [19, 20], and HZ vaccination is highly effective for HZ [21]. In our study, SARS-CoV-2 infection was identified from HER-SYS data and controlled by the study design (ie, exclusion criteria and censoring). Although HZ vaccination data were not available in our study, confounding by HZ vaccination is believed to be very limited because of the extremely low coverage of HZ vaccines in Japan (SHINGRIX: approximately 0.02% among people aged ≥50 years) [22, 23].

Subgroup analysis by age showed an increased risk of HZ in the cohort aged <50 years. The results from the additional analysis suggest that age modifies the effect of the second vaccination. In a previous cohort study in Israel, with a relatively young population (median age, 37 years; IQR, 25–52), there was an increased risk of HZ (risk ratio 1.43; 95% CI, 1.2–1.73) [7]. The background incidence of HZ in the younger population was much lower than that in the elderly, because old age is a risk factor for HZ [17]. Thus, where any slight vaccine-induced effects on HZ occur, there is a tendency that the effect will be more likely detected in the younger population. However, the study conducted in the United States reported the results of a subgroup analysis by age, and no increased risk of HZ was observed in either age group (<50 years, IRR 0.92 [95% CI, 0.7–1.09]; ≥50 years, IRR 0.90 [95% CI, 0.7–1.04]) [8]. This discrepancy in the results of countries might have been caused by differences in regional background factors. In general, the incidence of HZ is lower in adults with greater contact with children in their daily lives, which is considered to be a surrogate for exposure to VZV and for a boost in immunity against it [24]. In Japan, the universal varicella vaccination program for children was introduced in 2014; the cumulative vaccination coverage among children aged 2 years has been very high at >94% since 2017 [25], showing a drastically reducing number of chickenpox cases in Japan [26]. On the other hand, the background incidence rate of HZ in Japan increased after 2014, especially among child-rearing generations in their 20s to 40s [27]. This is believed to be due to the reduced opportunity to activate parents' cellular immunity to varicella in their children. Lower cellular immunity in the child-rearing generation than that in other countries might be one of the reasons for the effect modification by age.

In the secondary analysis, there was an increased risk of HZ after day 29 of the first dose of BNT162b2. This risk period included only people who had delayed their second vaccination for more than 1 week longer than the expected vaccination schedule. Therefore, it is more likely that the reasons for the postponement of the second vaccination (ie, worsening health status) had an influence on the increased risk of HZ occurrence.

There are 2 possible mechanisms for COVID-19 vaccination and the development of HZ based on previous studies: attenuation of VZV-specific immunity and promotion of virus reactivation of VZV. The former potential mechanism is related to the ability of the BNT162b2 vaccine to elicit a robust humoral

Table 3. Subgroup Analysis by Sex, Age, and Municipality: Incidence Rate Ratios of Herpes Zoster Within 28 Days of BNT162b2 Vaccinations

Subgroup	Exposure	Number of Individuals	PY	Number of Outcomes	Rate/100 000 PY	Crude Rate Ratio[a] (95% CI)	Adjusted Rate Ratio[a,b] (95% CI)
Male	Unvaccinated period	143 361	112 778	461	409	Reference	Reference
	BNT162b2 first dose[c]	120 382	6979	25	358	0.88 (0.59–1.31)	0.82 (0.55–1.22)
	BNT162b2 second dose	119 245	9353	42	449	1.1 (0.80–1.51)	1.02 (0.74–1.40)
Female	Unvaccinated period	196 187	152 080	667	439	Reference	Reference
	BNT162b2 first dose[c]	169 460	9832	55	559	1.28 (0.97–1.68)	1.22 (0.92–1.60)
	BNT162b2 second dose	167 858	13 182	70	531	1.21 (0.95–1.55)	1.15 (0.90–1.47)
<50	Unvaccinated period	40 179	39 404	58	147	Reference	Reference
	BNT162b2 first dose[c]	24 633	1424	2	140	0.95 (0.23–3.91)	0.93 (0.23–3.81)
	BNT162b2 second dose	23 888	1756	8	456	3.09 (1.48–6.48)	2.94 (1.41–6.13)
≥50	Unvaccinated period	299 369	225 454	1070	475	Reference	Reference
	BNT162b2 first dose[c]	265 209	15 386	78	507	1.07 (0.85–1.34)	1.05 (0.84–1.33)
	BNT162b2 second dose	263 215	20 779	104	501	1.05 (0.86–1.29)	1.04 (0.85–1.27)
City A	Unvaccinated period	63 260	47 527	163	343	Reference	Reference
	BNT162b2 first dose[c]	56 184	3240	10	309	0.90 (0.48–1.70)	0.87 (0.46–1.64)
	BNT162b2 second dose	55 175	4723	11	258	0.75 (0.41–1.38)	0.71 (0.39–1.32)
City B	Unvaccinated period	70 906	57 547	197	342	Reference	Reference
	BNT162b2 first dose[c]	58 914	3434	14	408	1.19 (0.69–2.05)	1.14 (0.66–1.96)
	BNT162b2 second dose	58 485	4580	20	437	1.28 (0.81–2.02)	1.21 (0.76–1.93)
City C	Unvaccinated period	91 781	72 088	284	394	Reference	Reference
	BNT162b2 first dose[c]	77 408	4486	19	424	1.08 (0.68–1.71)	1.02 (0.64–1.63)
	BNT162b2 second dose	76 789	6063	35	577	1.47 (1.03–2.08)	1.39 (0.98–1.98)
City D	Unvaccinated period	113 601	87 696	484	552	Reference	Reference
	BNT162b2 first dose[c]	97 336	5650	37	655	1.19 (0.85–1.66)	1.11 (0.79–1.55)
	BNT162b2 second dose	96 654	7619	46	604	1.09 (0.81–1.48)	1.02 (0.75–1.38)

Abbreviations: CI, confidence interval; City A, Chugoku region; City B and C, Kanto region; City D, Chubu region; IRR, incidence rate ratio; PY, person-years.

[a]Estimated using Poisson regression model.

[b]Adjusted for age, sex, municipality, clinic or hospital visit count, rheumatic disease, kidney disease, liver disease, diabetes, cancer, acquired immune deficiency syndrome/human immunodeficiency virus, organ transplant, systemic corticosteroids, and immunosuppressants.

[c]When the second dose was administered within a 28-day interval of the first dose, the risk period ended on the day before the second dose was given.

and cellular immune response [28]. Such a strong, specific, immune response may disrupt the cell-mediated control of another latent virus. Psichogiou et al [29] suggested that a condition similar to an immune reconstitution inflammatory syndrome, in which opportunistic infections are paradoxically exacerbated when immunity improves after antiretroviral therapy for AIDS, may occur during the immune response after COVID-19 vaccination and increase the risk of developing HZ. The latter potential mechanism is related to the stimulation of innate immunity through Toll-like receptors (TLRs) by mRNA-based vaccines [30]. The TLR signaling has been implicated in the reactivation of herpesviruses [31]. Therefore, mRNA vaccines might stimulate a pathway involved in the reactivation of VZV.

This study has several limitations. First, the population is skewed toward the elderly. This is because the population included in the VENUS Study lacked company-based workers and dependents [15]. Consequently, the sample size of the subgroup aged <50 years was much less than that of the subgroup aged ≥50 years. In addition, the number of individuals receiving the mRNA-1273 vaccine, primarily administered to Japan's working population during the study period, was limited.

Further studies are needed for evaluation in younger age groups with larger sample sizes. Second, only the primary series of vaccination (first and second doses) was evaluated in this study, and the effect of booster vaccination was not evaluated. In Japan, booster vaccination has been available since December 2021, and bivalent vaccination has been available since September 2022. Further studies are needed to determine the impact of these booster vaccines. Third, our analysis was limited by the potential misclassification of the outcome because the algorithm identified for HZ onset was not validated. However, the validity of the algorithm was improved by including not only diagnostic codes but also prescription codes from a clinical perspective.

CONCLUSIONS

This population-based cohort study showed no increased risk of HZ after BNT162b2 vaccination, compared with that in the unvaccinated period in the overall study population. The analysis of mRNA-1273 was impossible due to the small sample size. In the subgroup analysis, an increased risk within 28 days after the second dose of BNT162b2 was found in the subgroup

aged <50 years, although the sample size was small and further evaluation is needed. These findings help guide decision making regarding COVID-19 vaccination and underscore the need for ongoing vaccine safety surveillance.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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