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MAJOR ARTICLE

Correlation of Postvaccination Fever With Specific Antibody Response to Severe Acute Respiratory Syndrome Coronavirus 2 BNT162b2 Booster and No Significant Influence of Antipyretic Medication

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Background. A severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccine booster elicits sufficient antibody responses that protect against coronavirus disease 2019, whereas adverse reactions such as fever have been commonly reported. Associations between adverse reactions and antibody responses have not been fully characterized, nor has the influence of antipyretic use.

Methods. This is a prospective observational cohort study in Japan, following our prior investigation of BNT162b2 2-dose primary series. Spike-specific immunoglobulin G (IgG) titers were measured for SARS-CoV-2–naive hospital healthcare workers who received a BNT162b2 booster. The severity of solicited adverse reactions, including the highest body temperature, and self-medicated antipyretics were reported daily for 7 days following vaccination through a web-based self-reporting diary.

Results. The data of 281 healthcare workers were available. Multivariate analysis extracted fever after the booster dose ($\beta = .305$, $P < .001$) as being significantly correlated with the specific IgG titers. The analysis of 164 participants with data from the primary series showed that fever after the second dose was associated with the emergence of fever after the booster dose (relative risk, 3.97 [95% confidence interval, 2.48–6.35]); however, the IgG titers after the booster dose were not associated with the presence or degree of fever after the second dose. There were no significant differences in the IgG titers by the use, type, or dosage of antipyretic medication.

Conclusions. These results suggest an independent correlation between mRNA vaccine–induced specific IgG levels and post–booster vaccination fever, without any significant influence of fever after the primary series. Antipyretic medications for adverse reactions should not interfere with the elevation of specific IgG titers.

Keywords. antipyretic; antibody; reactogenicity; SARS-CoV-2; vaccine.

Administration of a messenger RNA (mRNA) coronavirus disease 2019 (COVID-19) vaccine has shown high vaccine efficacy, substantially reducing the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the development of severe or critical disease [1–4]. These efficacy data are consistent with evidence from immunogenicity studies that show robust specific antibody responses to the mRNA COVID-19 vaccines [5, 6]. It is notable that the specific immunoglobulin G (IgG) and neutralization titers of vaccinees who received an mRNA COVID-19 vaccine exceeded those of recovered COVID-19 patients [7, 8]. On the other hand, the reactogenicity of mRNA COVID-19 vaccines is known to be relatively high, and fever is a common adverse reaction. Around 15% of vaccinees had fever after the second or third dose of an mRNA COVID-19 vaccine [1, 9, 10], while only 1%–2% did so after influenza or pneumococcal vaccination [11, 12]. The possible relation between adverse reactions, including fever, and the antibody responses to mRNA COVID-19 vaccines remains to be fully elucidated. Antipyretic or pain medications (antipyretics) are often used to mitigate the frequent adverse events. Public health authorities allow the use of antipyretics in response to adverse events [13, 14], but data for the possible influence of their use on the antibody responses to COVID-19 vaccines are insufficient.

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We previously investigated the correlation of adverse reactions with the specific antibody responses to the 2-dose primary series of BNT162b2 vaccine (Pfizer/BioNTech). The influence of antipyretic use on antibody responses was also investigated. A positive correlation of degree of fever after the second dose and little interference from the antipyretic medications on the antibody titers were shown [15]. In the present study of the same cohort, we prospectively investigated the association of adverse reactions, which were evaluated using a standardized assessment tool, and the use of antipyretics with the specific antibody responses to a booster dose of BNT162b2 vaccine. In addition, using the data of the participants for whom information on both the second and booster doses was available, we also evaluated whether the specific antibody titers after the booster dose are affected by fever after the second dose.

METHODS

Participants

Eligible participants were healthcare workers who received three 30-μg doses of BNT162b2 at Fukuoka City Hospital in Japan. The primary 2-dose vaccine series with a 21-day interval was administered between March and June 2021, and the booster dose was given between December 2021 and January 2022. Included in the analysis were vaccinees who had serum sampling done ≥14 days after the booster dose and who completely responded to questionnaires about their background and solicited adverse reactions. The exclusion criteria were (1) previous laboratory-confirmed COVID-19 diagnosis, (2) positive results for antibodies targeting the viral nucleocapsid protein [IgG(N)], (3) the use of an antipyretic within 24 hours before the booster dose, and (4) receipt of immunosuppressive therapy.

Participant Consent Statement

All participants provided written informed consent before undergoing any of the study procedures. The study was approved by the ethics review board of Fukuoka City Hospital (approval number 228) and registered in the University Hospital Medical Information Network Clinical Trials Registry (registration number UMIN000046246).

Demographic Characteristics, Reactogenicity, and Antipyretic Medications

Participant background information was collected by a web-based questionnaire. Local and systemic adverse reactions were reported daily for 7 days after the booster dose through a web-based self-reporting diary. The solicited data were as follows: (1) local reactions (pain at the injection site, redness, and swelling) and (2) systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, joint pain, and lymphadenopathy). Axillary body temperature was measured twice daily, morning and night, and whenever the participant felt feverish. The highest body temperature during the 7 days was used in the analysis. All solicited reactions except lymphadenopathy were recorded based on standardized assessment scales developed by the US Food and Drug Administration guidelines [16]. Lymphadenopathy was evaluated for its presence or absence. The use of an antipyretic was left up to the participant. Information on the self-medicated antipyretics, including name, dosage, timing, and reason for use, was collected daily with the solicited adverse reactions for the 7 days after the booster dose.

Previously collected data on the receptor-binding domain of the S1 subunit of the viral spike protein (S-RBD) IgG titers and adverse reactions to the second dose were used in the present study. The major differences in the method of data collection were that in the earlier studies the adverse reaction information was collected for 5 days, not 7, after each of the doses and that we had used an originally defined subjective scaling method, except for fever. The detailed methods are shown in our previous study [15].

Serological Testing

Serum samples were collected twice, before and after the booster dose. The interval between the booster dose and the sampling after vaccination was scheduled at approximately 1 month to match it with the interval between the second dose and the sampling [15]. The quantitative levels of IgG(S-RBD) and IgG(N) were measured using the SARS-CoV-2 IgG II assay and SARS-CoV-2 IgG assay, respectively (Abbott Laboratories, Abbott Park, Illinois). Signal-to-cutoff values of ≥1.4 AU/mL were applied for IgG(N) positivity [17].

Statistical Analysis

The IgG(S-RBD) titers were log-transformed for analysis. The median with interquartile range (IQR), geometric mean titer (GMT), fold change, 95% confidence interval (CI), and relative risk (RR) were calculated. Between-group differences were calculated with Student *t* test, analysis of variance, or post hoc Dunnett test in line with suitability. Correlation coefficients were calculated using Spearman correlation coefficient. Multivariate linear regression models with a stepwise selection procedure were established. Multicollinearity among variables was examined using variance inflation factors. The level of significance was set at <5%, 2-sided. All analyses were performed using the SAS software package, release 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

Demographic Characteristics

Among 419 staff members who received the BNT162b2 booster, serum samples were collected from 346, and 316 satisfied the inclusion criteria. Of these, 13 were excluded due to a history of COVID-19 or IgG(N) ≥1.4 AU/mL, 20 due to

prevaccination use of antipyretics, and 2 due to having received immunosuppressive therapy, leaving the data of 281 participants available for analysis. Demographic and background information are summarized in Table 1. The median age was 41 years (IQR, 33–50 years), 72.6% were female, all were Japanese, and 77.2% had no coexisting conditions. The median interval between the second and booster doses was 262 days (IQR, 260–264 days; range, 219–288 days). Serum samples before and after the booster dose were obtained approximately 8 months after the second dose (median, 247 days [IQR, 244–252 days]) and 1 month after the booster dose (median, 32 days [IQR, 29–33 days]), respectively.

IgG(S-RBD) Titer and Fold Change by Demographic Characteristics

The booster dose increased the GMT of IgG(S-RBD) 29.4-fold (95% CI, 26.7–32.5), from 573 AU/mL (95% CI, 528–621) to 16 707 AU/mL (95% CI, 15 403–18 122). The IgG(S-RBD) titers and fold changes according to demographic characteristics are shown in Table 1. In the analysis of the IgG(S-RBD) titers, sex and age showed no significant correlation ($P = .197$ and $P = .645$, respectively). In contrast, both were significantly correlated with the fold changes. The mean fold change in males was higher than that in females (36.7-fold [95% CI, 31.1–43.3] vs 26.7-fold [95% CI, 24.4–29.3]; $P < .001$). Age showed a positive correlation with the fold changes ($r = 0.244$, $P < .001$). Comorbidities other than diabetes were not correlated. Diabetes had statistically significant correlations with both the IgG(S-RBD) titers and fold changes, but it was not further analyzed due to the small number of participants with diabetes.

IgG(S-RBD) Titer and Fold Change by Adverse Reaction

The IgG(S-RBD) titers and fold changes after the booster dose by the solicited adverse reactions are shown in Table 2. None of the local reactions had a significant correlation with the IgG(S-RBD) titers. Among the systemic reactions, fever showed a positive correlation with the IgG(S-RBD) titers ($r = 0.262$, $P < .001$). Fatigue ($P = .022$), headache ($P = .024$), chills ($P = .001$), and lymphadenopathy ($P < .001$) were also positively correlated. Neither local nor systemic adverse reactions significantly affected the fold changes in IgG(S-RBD) titers.

Factors that showed a P value of <.2 in the univariate analyses, including sex, body mass index, smoking history, heart disease, fever, fatigue, headache, chills, vomiting, and lymphadenopathy, were incorporated in the multivariate analysis. Among these variables, only fever (standardized regression coefficient: $\beta = .305$ [95% CI, .193–.417]; $P < .001$) was extracted as being independently correlated with the IgG(S-RBD) titers (adjusted $R^2 = 0.090$). A similar analysis for the fold change in IgG(S-RBD) titers extracted age ($\beta = .248$ [95% CI, .136–.360]; $P < .001$), male sex ($\beta = .183$ [95% CI, .071–.294]; $P = .001$), and fever ($\beta = .136$ [95% CI, .024–.248]; $P = .018$) as significant (adjusted $R^2 = 0.105$). All variance inflation values were <5 in the linear regression models, indicating the absence of multicollinearity among the factors.

Influence of Antipyretic Medications on IgG(S-RBD) Titer and Fold Change

The analyses of the influence of antipyretics on the IgG(S-RBD) titers and fold changes are shown in Table 3. In total, 119 (42.4%) participants used antipyretics during the 7 days after the booster dose. None of the participants prophylactically used an antipyretic after the vaccination to prevent adverse events. The GMT of IgG(S-RBD) was comparable between the groups with and without antipyretic use (17 466 AU/mL [95% CI, 15 279–19 966] vs 16 170 AU/mL [95% CI, 14 601–17 906]; $P = .357$). Similarly, there was no significant difference in the mean fold change between the 2 groups (29.4-fold [95% CI, 26.1–33.2] vs 28.9-fold [95% CI, 25.9–32.4]; $P = .893$). No significant influence of antipyretic use was found when stratified by fever grade, classified into <37.0°C, 37.0°C–37.9°C, and ≥38.0°C. The most commonly used antipyretic combination was acetaminophen monotherapy (43/119 [36.1%]), followed by loxoprofen monotherapy (35/119 [29.4%]) and ibuprofen monotherapy (14/119 [11.8%]). The IgG(S-RBD) titers and fold changes of the group with nonsteroidal anti-inflammatory drugs (NSAIDs) such as loxoprofen and ibuprofen were comparable to those of acetaminophen. The IgG(S-RBD) titers by all combinations of antipyretics used are summarized in Supplementary Table 1.

Association Between the Presence or Absence of an Adverse Reaction After the Second Dose and the Emergence of the Same Reaction After the Booster Dose

Using the data of 164 participants for whom information on both the second and booster doses were available, the probability of a solicited adverse reaction after the booster dose was investigated by the presence or absence of the corresponding reaction after the second dose (Table 4). The RR of all solicited adverse reactions was >1.0. The presence of swelling at the injection site, fever of ≥38.0°C, headache, chills, muscle pain, and joint pain after the second dose showed a significant association with the emergence of the corresponding reaction after the booster dose. The RR was the highest for the fever, at 3.97 (95% CI, 2.48–6.35).

IgG(S-RBD) Titer by the Presence of Fever After the Second and Booster Doses

The 164 participants were divided into 4 groups by the presence or absence of fever of ≥38.0°C after each dose. The IgG(S-RBD) titers of these 4 groups 1 month after the second dose, 8 months after the second dose, and 1 month after the booster dose are shown in Table 5. The GMTs of IgG(S-RBD) 1 month after the second dose were higher for the groups with fever after the second dose than for those without. Eight months after the second dose, the differences among the groups were subtle, ranging from 537 to 796 AU/mL, without significant

Table 1. Demographic Characteristics, Spike Receptor-Binding Domain Immunoglobulin G Titer, and Fold Change

		IgG(S-RBD) Titers Before Dose 3		IgG(S-RBD) Titers After Dose 3		Change in Titers After Dose 3	
Characteristic	No. (%)	GMT (95% CI), AU/mL	*P* Value	GMT (95% CI), AU/mL	*P* Value	Fold Change, Mean (95% CI)	*P* Value
All eligible participants	281	573 (528–621)		16 707 (15 403–18 122)		29.4 (26.7–32.5)	
Sex							
Female	204 (72.6)	602 (546–665)	.047	16 110 (14 743–17 604)	.197	26.7 (24.4–29.3)	<.001
Male	77 (27.4)	502 (436–577)		18 395 (15 325–22 085)		36.7 (31.1–43.3)	
Age, y							
Median (IQR)	41 (33–50)	$r = -0.215$[a]	<.001	$r = 0.009$[a]	.877	$r = 0.231$[a]	<.001
<40	127 (45.2)	648 (582–723)	.014	16 970 (15 199–18 948)	.509	26.2 (23.4–29.3)	.006
40–54	118 (42.0)	534 (472–603)		15 937 (14 055–18 072)		29.9 (26.2–34.0)	
≥55	36 (12.8)	468 (345–634)		18 453 (13 623–24 995)		39.5 (30.7–50.7)	
Smoking							
Never	234 (83.3)	602 (549–659)	.030	17 249 (15 747–18 894)	.134	28.7 (26.2–31.4)	.473
Ex-smoker	26 (9.3)	457 (385–543)		15 627 (12 922–18 899)		34.2 (27.8–42.1)	
Current smoker	21 (7.5)	441 (321–605)		12 713 (9214–17 540)		28.8 (21.3–39.1)	
Alcohol use							
None	113 (40.2)	598 (523–684)	.493	17 781 (15 604–20 261)	.465	29.7 (26.4–33.4)	.698
Sometimes	136 (48.4)	569 (510–634)		16 048 (14 358–17 937)		28.2 (25.0–31.8)	
Almost every day	32 (11.4)	508 (378–682)		15 907 (11 890–21 282)		31.3 (23.0–42.5)	
BMI, kg/m^2							
Median (IQR)	21.2 (19.7–23.3)	$r = -0.032$[a]	.599	$r = .091$[a]	.130	$r = .137$[a]	.022
<18.5	26 (9.3)	531 (373–758)	.417	15 055 (11 162–20 307)	.545	27.2 (20.7–35.7)	.079
18.5–24.9	220 (78.6)	589 (539–645)		16 666 (15 268–18 192)		28.3 (25.8–31.0)	
≥25.0	34 (12.1)	506 (408–682)		18 332 (15 695–24 540)		39.9 (32.2–44.5)	
Job category							
Nurse	140 (49.8)	575 (516–641)	.483	15 704 (14 270–17 283)	.488	27.3 (24.7–31.2)	.061
Clerk	40 (14.2)	648 (507–828)		15 731 (12 771–19 378)		24.3 (18.8–31.3)	
Doctor	30 (10.7)	467 (362–602)		17 364 (12 091–24 936)		37.2 (27.3–50.7)	
Radiologist	13 (4.6)	605 (438–837)		19 694 (12 239–31 690)		32.5 (17.7–59.8)	
Pharmacist	12 (4.3)	652 (389–1093)		19 696 (14 270–17 283)		30.2 (18.3–49.9)	
Other	46 (16.4)	555 (443–694)		18 953 (15 130–23 742)		34.2 (28.4–41.1)	
Comorbidities							
Allergic rhinitis							
Yes	43 (15.3)	537 (448–645)	.508	14 801 (11 989–18 277)	.213	27.6 (23.2–32.7)	.563
No	238 (84.7)	580 (530–635)		16 963 (15 513–18 548)		29.4 (26.7–32.5)	
Dislipidemia							
Yes	17 (6.1)	656 (464–929)	.405	20 333 (12 526–33 007)	.381	31.0 (21.7–44.3)	.710
No	264 (94.0)	568 (522–618)		16 497 (15 205–17 898)		29.0 (26.7–31.6)	
Hypertension							
Yes	14 (5.0)	455 (262–790)	.364	12 314 (6393–23 719)	.313	27.1 (18.0–40.7)	.683
No	267 (95.0)	580 (535–629)		16 975 (15 678–18 382)		29.3 (26.9–31.8)	
Asthma							
Yes	5 (1.8)	798 (470–1352)	.281	21 154 (11 389–39 292)	.442	26.5 (15.4–45.8)	.759
No	276 (98.2)	570 (525–618)		16 634 (15 321–18 063)		29.2 (26.9–31.7)	
Diabetes							
Yes	3 (1.1)	439 (96–2004)	.504	41 850 (14 723–118 987)	.021	95.3 (56.1–162.0)	.003
No	278 (98.9)	575 (529–624)		16 542 (15 251–17 943)		28.8 (26.5–31.2)	
Heart disease							
Yes	3 (1.1)	539 (324–894)	.876	33 411 (3446–323 966)	.081	62.0 (6.1–632.8)	.058
No	278 (98.9)	573 (528–622)		16 581 (15 290–17 985)		28.9 (26.7–31.4)	
Malignancy							
Yes	3 (1.1)	460 (45–4648)	.581	19 838 (1219–322 849)	.666	43.1 (3.7–497.3)	.327
No	278 (98.9)	574 (529–623)		16 676 (15 374–18 088)		29.0 (26.8–31.5)	
Chronic kidney disease							
Yes	1 (0.4)	626 (NA)	NA	32 300 (NA)	NA	51.6 (NA)	NA
No	280 (99.4)	573 (528–621)		16 669 (15 364–18 080)		29.1 (26.8–31.6)	

Abbreviations: BMI, body mass index; CI, confidence interval; GMT, geometric mean titer; IgG(S-RBD), immunoglobulin G spike receptor-binding domain; IQR, interquartile range; NA, not available.

[a] *r* values refer to the Spearman correlation coefficient.

Table 2. Influence of Adverse Reaction Variables on Spike Receptor-Binding Domain Immunoglobulin G Titer

Reaction	Variable	No. (%)	GMT (95% CI), AU/mL	*P* Value	Fold Change, Mean (95% CI)	*P* Value
Local reactions						
Pain at injection site	No	3 (1.1)	14 818 (4032–54 450)	.763	23.9 (10.9–52.4)	.618
	Yes	278 (98.9)	16 730 (15 413–18 155)		29.2 (26.9–31.7)	
Redness	No	185 (65.8)	16 761 (15 198–18 484)	.915	28.9 (26.2–31.9)	.734
	Yes	96 (34.2)	16 604 (14 328–19 244)		29.7 (25.7–34.4)	
Swelling	No	148 (52.7)	16 707 (14 866–18 772)	.998	30.5 (27.4–33.8)	.269
	Yes	133 (47.3)	16 707 (14 907–18 728)		27.8 (24.5–31.6)	
Systemic reactions						
Fever	Absolute value	281 (100)	$r = 0.262$[a]	<.001	$r = 0.082$[a]	.170
	<37.0°C	114 (40.6)	14 011 (12 431–15 793)	<.001	26.9 (23.7–30.5)	.100
	37.0°C–37.9°C	97 (34.5)	16 302 (14 174–18 750)		28.8 (25.3–32.9)	
	≥38.0°C	64 (24.9)	23 020 (19 670–26 941)		33.7 (28.1–40.5)	
Fatigue	No	42 (15.0)	13 329 (10 713–16 581)	.022	26.2 (20.8–32.9)	.278
	Yes	239 (85.1)	17 382 (15 933–18 967)		29.7 (27.2–32.4)	
Headache	No	94 (33.5)	14 652 (12 885–16 661)	.024	29.3 (25.6–33.5)	.947
	Yes	187 (66.6)	17 848 (16 099–19 783)		29.1 (26.3–32.3)	
Chills	No	135 (48.0)	14 534 (13 077–16 151)	.001	27.3 (24.3–30.7)	.126
	Yes	146 (52.0)	19 006 (16 862–21 419)		31.0 (27.6–34.8)	
Vomiting	No	272 (96.8)	16 512 (15 198–17 943)	.121	29.1 (26.7–31.6)	.721
	Yes	9 (3.2)	23 752 (16 021–35 221)		31.6 (22.5–44.5)	
Diarrhea	No	246 (87.5)	16 811 (15 385–18 365)	.693	29.3 (26.8–32.0)	.812
	Yes	35 (12.5)	15 999 (13 005–19 683)		28.4 (23.6–34.2)	
Muscle pain	No	40 (14.2)	17 434 (14 142–21 493)	.674	28.9 (22.2–37.7)	.944
	Yes	241 (85.8)	16 588 (15 181–18 126)		29.2 (26.8–31.8)	
Joint pain	No	128 (45.6)	16 044 (14 315–17 980)	.370	27.9 (24.6–31.6)	.335
	Yes	153 (54.5)	17 282 (15 396–19 404)		30.2 (27.1–33.7)	
Lymphadenopathy	No	194 (69.0)	15 332 (13 845–16 975)	<.001	29.1 (26.1–32.4)	.956
	Yes	87 (31.0)	20 234 (17 857–22 935)		29.2 (26.2–32.7)	

Abbreviations: CI, confidence interval; GMT, geometric mean titer.

[a] *r* values refer to the Spearman correlation coefficient.

differences. The GMTs of IgG(S-RBD) 1 month after the booster dose were higher in the groups with fever after the booster dose, and they were comparable between the groups with and without fever after the second dose. A multivariate analysis incorporating fever after the second dose was additionally done. Fever after the booster dose was extracted as being significantly correlated with the IgG(S-RBD) titers after the booster dose ($\beta = .246$ [95% CI, .097–.395]; $P = .001$), but fever after the second dose was not.

DISCUSSION

A booster dose of an mRNA COVID-19 vaccine induces a higher antibody titer than is produced by the primary 2-dose series [18, 19]. Our previous study showed that the IgG(S-RBD) titers after the second dose of the primary series were relatively low for male participants and the elderly [15], as shown in other studies [20, 21]. In contrast, in the present study of the booster dose for the same cohort, male sex and age showed positive correlations with the fold change in IgG(S-RBD) titers, reaching comparable levels in the IgG(S-RBD) titers by sex and age. Other studies have also shown that the specific IgG titers after the BNT162b2 booster were comparable for sex and age [22, 23]. The mechanism for the difference in the immunogenicity of a BNT162b2 vaccine by sex and age between the second and booster doses is unclear, but the booster vaccination would drive antibody production, especially in the populations with relatively weak responses to the primary series.

The relation between the emergence of vaccine-related adverse reactions and antibody induction by the primary series of mRNA COVID-19 vaccines has been reported. Studies that used scores based on the sum of the presence or a severity scale of solicited adverse reactions showed no significant correlation of adverse reactions with the spike-specific IgG titers [24–26]. On the other hand, when each reaction was separately analyzed, the presence of fever after the second dose was shown to be correlated with high IgG titers [27, 28]. We previously showed that degree of fever after the second dose was correlated with the IgG(S-RBD) titers by a multivariate analysis [15]. In the present study, the degree of fever after the booster dose, which was defined by the highest body temperature after the vaccination, was again shown to have a significant correlation with the IgG(S-RBD) titers. Note that the clinical significance

Table 3. Influence of Antipyretics on Spike Receptor-Binding Domain Immunoglobulin G Titer and Fold Change After a Booster Dose

Characteristic		No. (%)	GMT (95% CI)	*P* Value	Fold Change, Mean (95% CI)	*P* Value
Use of antipyretic medications						
All participants	No	162 (57.7)	16 170 (14 601–17 906)	.357	28.9 (25.9–32.4)	.893
	Yes	119 (42.4)	17 466 (15 279–19 966)		29.4 (26.1–33.2)	
By fever grade						
<37.0°C	No	85 (74.6)	14 217 (12 491–16 181)	.681	27.8 (23.8–32.4)	.400
	Yes	29 (25.4)	13 425 (10 006–18 009)		24.6 (19.9–30.3)	
37.0°C–37.9°C	No	50 (51.6)	16 489 (13 602–19 985)	.869	30.0 (24.7–36.4)	.556
	Yes	47 (48.5)	16 106 (13 041–19 893)		27.7 (23.2–33.2)	
≥38.0°C	No	27 (38.6)	23 388 (17 914–30 542)	.874	31.0 (22.4–42.8)	.465
	Yes	43 (61.4)	22 793 (18 612–27 906)		35.6 (28.3–44.6)	
Type of antipyretic						
Only acetaminophen	…	43 (36.1)	17 132 (13 886–21 136)	Reference	26.3 (21.3–32.5)	Reference
Only loxoprofen	…	35 (29.4)	14 820 (11 167–19 669)	.744	25.4 (2.6–31.2)	.991
Only ibuprofen	…	14 (11.8)	20 306 (13 383–30 811)	.815	41.2 (28.5–59.7)	.068
Other[a]	…	27 (22.7)	20 613 (15 651–27 149)	.637	35.9 (28.3–45.6)	.135
Total dosage of antipyretic during 7-days after vaccination						
Acetaminophen, mg, median (IQR)		900 (400–1200)	$r = 0.072$[b]	.648	$r = .247$[b]	.111
Loxoprofen, mg, median (IQR)		120 (60–180)	$r = 0.097$[b]	.580	$r = .223$[b]	.198
Ibuprofen, mg, median (IQR)		200 (150–400)	$r = -0.346$[b]	.226	$r = -.201$[b]	.491
Timing of antipyretic use						
Antipyretic use on the day of vaccination	No	108 (90.8)	17 151 (14 856–19 797)	.398	30.0 (26.4–34.1)	.308
	Yes	11 (9.2)	20 903 (14 378–30 395)		24.3 (16.9–34.9)	

Abbreviations: CI, confidence interval; GMT, geometric mean titer; IQR, interquartile range.

[a]Including other type of antipyretics, combination drugs, or combination of several antipyretics.

[b]*r* values refer to the Spearman correlation coefficient.

Table 4. Probability of an Adverse Reaction After the Booster Dose According to the Presence or Absence of the Same Reaction After the Second Dose

Adverse Reaction		Corresponding Reactions After Booster Dose		Incidence of a Corresponding Reaction After Booster Dose, %	RR (95% CI)
		Present	Absent		
Local reactions after dose 2					
Pain at injection site	Present	154	1	99.4	1.12 (.89–1.41)
	Absent	8	1	88.9	Reference
Redness	Present	14	16	46.7	1.56 (.98–2.48)
	Absent	40	94	29.9	Reference
Swelling	Present	45	23	66.2	1.93 (1.39–2.66)
	Absent	33	63	34.4	Reference
Systemic reactions after dose 2					
Fever ≥38.0°C	Present	21	12	63.6	3.97 (2.48–6.35)
	Absent	21	110	16.0	Reference
Fatigue	Present	129	14	90.2	1.35 (1.00–1.84)
	Absent	14	7	66.7	Reference
Headache	Present	80	19	80.8	1.46 (1.15–1.85)
	Absent	36	29	55.4	Reference
Chills	Present	52	18	74.3	2.00 (1.48–2.68)
	Absent	35	59	37.2	Reference
Diarrhea	Present	3	17	15.0	1.14 (.37–3.50)
	Absent	19	125	13.2	Reference
Muscle pain	Present	85	6	93.4	1.22 (1.06–1.40)
	Absent	56	17	76.7	Reference
Joint pain	Present	59	21	73.8	1.77 (1.33–2.35)
	Absent	35	49	41.7	Reference

Information on vomiting and lymphadenopathy after the second dose were not collected.

Abbreviations: CI, confidence interval; RR, relative risk.

Table 5. Spike Receptor-Binding Domain Immunoglobulin G Titers by the Presence or Absence of Fever After the Second and Booster Doses

Fever ≥38.0°C After Vaccination (After Dose 2/Dose 3)	No. (%)	Female Sex, No. (%)	Age, y, Median (IQR)	1 Month After Dose 2		8 Months After Dose 2		1 Month After Dose 3	
				GMT (95% CI), AU/mL	*P* Value	GMT (95% CI), AU/mL	*P* Value	GMT (95% CI), AU/mL	*P* Value
Absent/Absent	110 (67.1)	83 (75.5)	42.0 (33.0–49.0)	8281 (7305–9386)	Reference	537 (474–607)	Reference	15 438 (13 665–17 441)	Reference
Present/Absent	12 (7.3)	9 (75.0)	33.5 (29.0–39.5)	12 026 (8204–17 628)	.169	796 (552–1147)	0.144	14 644 (10 630–20 174)	.990
Absent/Present	21 (12.8)	12 (57.1)	41.0 (46.0–51.0)	9172 (6717–12 524)	.879	738 (515–1058)	0.125	22 012 (16 555–29 270)	.060
Present/Present	21 (12.8)	17 (81.0)	40.0 (28.0–44.0)	12 343 (9562–15 932)	.032	627 (481–817)	0.682	22 479 (16 575–30 487)	.042

Abbreviations: CI, confidence interval; GMT, geometric mean titer; IQR, interquartile range.

of the difference in the IgG(S-RBD) titers due to postvaccination fever (eg, the GMTs for the participants with fever of <37.0°C and ≥38.0°C were 14 011 AU/mL and 23 020 AU/mL, respectively) for protection against SARS-CoV-2 infection is difficult to evaluate. In general, the IgG(S-RBD) titers measured with the assay used in our study were shown to be correlated with the neutralizing antibody levels, a surrogate marker for protection, although the correlation at relatively high IgG(S-RBD) titers, as detected in our study, has been inconsistent across studies [29–31]. A positive correlation was reported not only for wild-type virus but also for variants including B.1.617.2 (Delta) and B.1.1.529 (Omicron) [32]. The mechanism of how fever after SARS-CoV-2 mRNA vaccination is linked to antibody production remains unclear. Elucidating the mechanism will lead to a better understand of the sufficient antibody induction mechanism of mRNA COVID-19 vaccines.

The possibility of a relation between postvaccination fever and the SARS-CoV-2–specific antibody titers has created concern that antipyretics, which can suppress fever, may have a negative influence on antibody responses to SARS-CoV-2 vaccination. To date, few studies have been done to determine the influence of antipyretics on the immunogenicity of COVID-19 vaccines. We previously showed that the use of antipyretics for fever or other adverse reactions did not interfere with the antibody responses to the primary BNT162b2 series [15]. In the present study for the BNT162b2 booster, no influence of antipyretic use on the IgG(S-RBD) titers was observed again. Although several in vitro laboratory studies have demonstrated that NSAIDs inhibit several pathways leading to antibody responses [33–35], the IgG(S-RBD) titers of the group with NSAIDs were comparable to those of the group with acetaminophen. The present study was not designed to evaluate the influence by the type of antipyretics, but it is suggested that neither acetaminophen nor NSAIDs would interfere with the elevation of IgG(S-RBD) titers. Antipyretics may also be used prophylactically. One study of a COVID-19 adenoviral vector vaccine reported that prophylactic acetaminophen use reduced many adverse reactions without interfering with antibody responses [36]. There are no studies on the influence of prophylactic use of antipyretics on antibody responses to mRNA COVID-19 vaccines. Taken together, our results indicate that the use of antipyretics for emerging adverse events, regardless of the type, acetaminophen or NSAIDs, would be helpful for alleviating adverse reactions, including fever, without interfering with antibody responses to SARS-CoV-2 mRNA vaccination.

It would be of great interest for physicians to determine whether the presence of an adverse reaction after the 2-dose primary series is useful to predict the emergence of the corresponding reaction after the booster dose. In the present study, the presence of swelling as a local reaction and several systemic reactions, including fever after the second dose, was associated with the emergence of the corresponding reactions after the

booster dose. Fever after the second dose showed the highest RR of 3.97. Of interest, fever after the booster dose was independently correlated with the IgG(S-RBD) titers after the booster dose, irrespective of fever after the second dose. Thus, participants with fever after the second dose may be more likely to have fever after the booster dose, but fever after the second dose would not affect the antibody responses to the booster dose. To our knowledge, no investigations of the correlation between postvaccination fever and specific IgG levels have been done in the same cohort throughout the primary and booster vaccinations. These findings impress a potential linking of postvaccination fever with the antibody production induced by mRNA COVID-19 vaccines.

This study has some limitations that should be acknowledged. First, it is a single-center observational study with a relatively small sample size of 281 participants. Additionally, the population was relatively young and predominantly female. Second, the data collection methods for the solicited adverse reactions were slightly different between the second and booster doses. The data collection period for adverse reactions was 7 days after vaccination for the booster dose, whereas it was 5 days for the second dose. However, most common adverse reactions have been known to occur within a few days after vaccination [37]; thus, the difference would have little impact on our findings. Finally, the type, dosage, and timing of antipyretic usage were chosen by each participant and are thus arbitrary. Besides, this study has insufficient statistical power due to the relatively small sample size, which may have led to underestimation in the possible negative influence of antipyretic use on the antibody responses. Large-scale randomized controlled studies will be necessary to clarify the influence of antipyretics on the immunogenicity outcomes of COVID-19 vaccines, but we believe that our real-world data from healthcare workers with self-medicated antipyretics is informative.

In conclusion, a booster dose of BNT162b2 vaccine can restore waning immunity and significantly increase the antibody titers, especially in males and the elderly who had relatively low antibody responses to the primary 2-dose series. Post–booster vaccination fever could be independently correlated with mRNA vaccine–induced specific IgG levels, without any significant influence of fever after the primary series. Although the relatively small sample size in this study means that our results are inconclusive, they indicate that antipyretic medications would be helpful to alleviate suffering from adverse reactions, without suppressing the specific IgG responses induced by a BNT162b2 vaccine booster.

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.

Notes

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