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Gulumbe, S. U., Suleiman, S., Ahmad, S. S., Hamza, M. M

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Early Detection of Safety Signal for COVID-19 Vaccine Safety Surveillance

Gulumbe, S. U.[1], Suleiman, S.[2], Ahmad, S. S.[2*], and Hamza, M. M[1].
[1]Department of Statistics, Usmanu Danfodiyo University, Sokoto, Nigeria
[2]Department of Mathematics and Statistics, Federal University Dutsin-Ma, Katsina State, Nigeria
*Corresponding Author's E-mail: salimahmadsalim36@gmail.com

Abstract

Early detection of adverse events is crucial in vaccine safety surveillance, especially for rare events often missed in pre-licensure clinical trials due to limited sample sizes. To address the challenge of vaccine safety monitoring and early signal detection, we conducted a comprehensive safety surveillance study utilizing Poisson and Binomial-based MaxSPRT methods. For Guillain-Barré Syndrome (GBS) and anaphylaxis, we employed the PMaxSPRT model due to their rarity, while for syncope and seizures; the Binomial-based MaxSPRT was applied. Using PMaxSPRT, no signal was detected for GBS, emphasizing the vaccine's safety in this regard. However, a signal for anaphylaxis was generated in the twelfth month, indicating a potential association. Employing the Binomial model, we found signals for both seizures and syncope.

Keywords: Adverse events, Signal detection, Relative risk, Surveillance, Sequential probability.

1. Introduction

Due to the urgent need to curb the further spread of COVID-19 infection, the standard procedure for new medicine and vaccine approval was circumvented in order to grant emergency approval for COVID-19 vaccines. Hence, post-vaccination adverse event surveillance is necessary (Kaur *et al*., 2021). The pattern and severity of adverse events following vaccinations may vary depending on geography, despite the fact that the safety of this vaccine has been thoroughly investigated. The possibility of unreported adverse events is also taken into account (Tequare *et al.*, 2021). Studying post-vaccination adverse effects in various populations and regions of the world is therefore necessary (Odeigah *et al*., 2022). Safety surveillance refers to the ongoing evaluation of a vaccine's safety following approval. A decision rule is used in a vaccine safety surveillance system to produce safety signals. Natural goals of a safety surveillance method are to control the rates of false positive and false negative signals, as well as to generate a signal as soon as possible when an association between the vaccine and adverse event exists.

The early detection of unexpected adverse events is crucial in vaccine safety surveillance. Adverse events (AEs), especially rare ones, may go undetected in pre-licensure clinical trials due to limited sample sizes. Consequently, post-approval continuous monitoring of vaccine safety in the larger population is essential. This will allows for prompt identification of serious and non-serious adverse events. Sequential analyses are conducted as data accumulates to ensure the earliest possible detection of any unexpected increased risk. To address the challenge of vaccine safety monitoring and early detection of safety signals, the Maximized Sequential Probability Ratio Test (MaxSPRT) was developed by Kulldorff *et al.* in 2011 as part of a project run by the Centers for Disease Control and Prevention. The Poisson maximized sequential probability ratio test (PMaxSPRT) and the Binomial sequential probability ratio test (BMaxSPRT) are the most popular variants of the MaxSPRT.

The Maximized SPRT was designed for drug and vaccine safety surveillance and has been used in various medical research studies. For instance, Kulldorf *et al*. (2011) analyzed Pediatric vaccine data to assess the increased risk of fever or neurological symptoms after Pediarix vaccination. Similarly, Li *et al.* (2019) investigated an increased risk of febrile seizures following the administration of the trivalent inactivated Influenza vaccine using classical SPRT

and Poisson-based MaxSPRT. Lloyd *et al*. (2022) focused on serious adverse events in COVID-19 vaccine recipients aged 12 to 64 years, using the Poisson-based MaxSPRT.

However, monitoring non-serious adverse events is crucial as they may signal potential problems with the vaccine or impact vaccine acceptability. Moreover, the BMaxSPRT has the advantage of having a much more relevant comparator, which should be less prone to bias. This paper aimed to address this gap by applying both Poisson and Binomial-based Maximized Sequential Probability Ratio Tests, to detect and evaluate early signals of adverse events associated with COVID-19 vaccinations, focusing on Guillain-Barré Syndrome (GBS), anaphylaxis, syncope and seizure. These complementary approaches will enhance the understanding of adverse events following Covid-19 vaccinations, considering both serious and non-serious events. The two competing hypothesis are the null and alternative; the former states that COVID-19 vaccine does not increases the risk of the pre-specified adverse events while the later suggest that it does.

2.0 Material and methods

The solution to the problem of hypothesis testing in a setting where observations arrive sequentially was developed by Wald (1945) during the Second World War and is known as sequential analysis. A sequential test of a statistical hypothesis is, according to Wald, a test process that provides a rule for deciding between three possible alternatives during a single trial of the experiment: accept the null hypothesis, reject the null hypothesis or continue the experiment by making an additional observation. A signal is generated if the likelihood ratio exceeds a certain predetermined value, and the observation ends if the likelihood falls below another predetermined lower bound.
This approach is of limited practical value for the assessment of an unknown vaccine risk; the simple alternative requires the magnitude R of the elevated risk to be known, which is usually not the case as one is merely interested in an unknown elevated risk RR. Therefore, it is difficult to apply the Wald's classical sequential probability ratio test (SPRT) for continuous monitoring as it is highly sensitive to the relative risk choice that is used in the specification of the alternative hypothesis. Instead, Kulldorf *et al*. (2011) recommend using a maximized sequential probability ratio test (MaxSPRT) based on a composite alternative hypothesis rather than simple, with the relative risk defined as being greater than one rather than a specific value. The MaxSPRT was developed in response to direct vaccine safety surveillance needs in the Centers for Disease Control and Prevention (CDC)-sponsored Vaccine Safety Datalink (VSD) and, as such, it is already in practical use. The MaxSPRT was explored for two different probability models using the Poisson and binomial distributions and termed as PMaxSPRT and BMaxSPRT respectively.

2.1 Poisson Modal: PMaxSPRT

Let X_t be the random variable representing the number of patients who have adverse events after a vaccination up to time t, and x_t be the corresponding observed number of patients who have experienced the adverse events, t represents the time when every new case is collected. Note that time is defined in terms of the time of the vaccination rather than the time of the adverse event. Under the null hypothesis H_0, X_t follows a Poisson distribution with a known mean μ_t, which is a known function, reflecting the population at risk. In our setting, μ_t reflects the number of people who received the COVID-19 vaccine during the time interval and a baseline risk for those individuals, adjusting for age and gender. Under the alternative hypothesis H_1, the mean is RR μ_t, where RR is the increased relative risk due to the vaccine. Note that $X_0 = x_0 = \mu_0 = 0$.

For Poisson modal, the MaxSPRT likelihood ratio based test is given as

$$LR_t = \frac{\max_{H_1} P\left(X_t = x_t \mid H_1\right)}{P\left(X_t = x_t \mid H_0\right)} \tag{1}$$

$$LR_t = \frac{\max_{RR>1} e^{-RR\mu_t} \left(RR\mu_t\right)^{x_t} \Big/ X_t!}{e^{-\mu_t} \mu_t^{x_t} \Big/ X_t!} \tag{2}$$

$$LR_t = \max_{RR>1} e^{(1-RR)\mu_t} (RR)^{x_t} \quad (3)$$

The MLE of RR, $\widehat{RR} = \frac{x_t}{\mu_t}$ when $x_t \geq \mu_t$,
so that,

$$LR_t = e^{\mu_t - x_t} \left(\frac{x_t}{\mu_t}\right)^{x_t}, \text{ when } x_t \geq \mu_t \quad (4)$$

and

$LR_t =$ 1 otherwise.

Equivalently when define using log-likelihood ratio

$$LLR_t = \ln(LR_t) \quad (5)$$

$$LLR_t = \left(\mu_t - x_t\right) + x_t \ln\left(\frac{x_t}{\mu_t}\right), \text{ when } x_t \geq \mu_t \quad (6)$$

and

$LR_t =$ 0 otherwise.

Where;
LLR_t is the log-likelihood ratio.
X_t is the random variable representing the number of patients who have adverse events after a vaccination up to time t.
x_t is the corresponding observed number of patients who have experienced the adverse events.
μ_t reflects the number of people who received the COVID-19 vaccine during the time interval and a baseline risk for those individuals.
RR is the increased relative risk due to the vaccine.
Again, the value obtained from the test statistic is compared to lower and upper critical values that have to be derived numerically. Exact critical values for a range of given α provided by Kulldorff*et al.* (2011).

2.2 Binomial Modal: BMaxSPRT

When events that occurred during the risk period are referred to as "cases" and those that occurred during the control period are referred to as "controls," the likelihood that an event will be classified as a case depends only on the risk ratio (RR) and the ratio of the two periods $Z = t_0 / t_1$.

(7)

The Probability of a "case" (defined as success) and "control" (defined as failure) are provided by

P ("case") = $P = \frac{RR}{RR + Z}$ (8)

P ("control") = $1 - P = \frac{Z}{RR + Z}$ (9)

Let n be the number of adverse events seen so far during the sequential data collection, and among those n events, let $x_n \leq n$ where x_n denotes the number of "cases" out of n events during the exposed time period, the probability distribution for x_n is given by the binomial distribution. The probability of "success" (i.e. adverse event classified as a "case"), depends on the unknown rate ratio parameter RR and the known ratio between the lengths of the

control and risk periods, z. Conditional on the number of adverse events n, we can then write the likelihood ratio for the binomial model as:

$$LR_n = \max_{H_1} \frac{P\left(X_n = x_n \mid H_1\right)}{P\left(X_n = x_n \mid H_0\right)} \tag{10}$$

$$LR_n = \max_{RR>1} \frac{\left[RR/(RR+Z)\right]^{x_n}\left[Z/(RR+Z)\right]^{n-x_n}}{\left[1/(1+Z)\right]^{x_n}\left[Z/(1+Z)\right]^{n-x_n}} \tag{11}$$

The MLE of RR, $\widehat{RR} = Zx_n/(n-x_n)$.

So that,

$$LR_n = \frac{\left(\frac{x_n}{n}\right)^{x_n}\left[(n-x_n)/n\right]^{n-x_n}}{\left[1/(Z+1)\right]^{x_n}\left[Z/(Z+1)\right]^{n-x_n}}, \text{ when } Zx_n/(n-x_n) > 1 \tag{12}$$

and

$LR_n = 1$ otherwise.

Equivalently defined using log-likelihood ratio

$$LLR_n = \ln(LR_n) \tag{13}$$

$$LLR_n = x_n \ln\left(\frac{x_n}{n}\right) + (n-x_n)\ln\left(\frac{n-x_n}{n}\right) - x_n \ln\left(\frac{1}{(Z+1)}\right) - (n-x_n)\ln\left(\frac{Z}{(Z+1)}\right) \tag{14}$$

when $LR_n = 0$ otherwise.

Where;

n is the number of adverse events seen so far during the sequential data collection.

LLR_n is the log-likelihood ratio.

X_n is the random variable representing the number of adverse events in risk and control periods.

x_n is the number of "cases" out of n events during the exposed time period.

3.0 Results

3.1 Sequential Analyses

We conducted a sequential analysis of Guillain-Barre Syndrome (GBS), anaphylaxis, syncope, and seizure, over a 24-month period. The critical values (CV) are given in the scale of the log-likelihood ratio (LLR) statistic. M = 4, z = 2. The maximum length of surveillance is 31.68 under a power-type alpha spending (ρ = 0.5) with alpha = 0.05. Sequential analysis of GBS cases over a 24-month period using PMaxSPRT was conducted as shown in Table 1. It has been found that the null hypothesis was not rejected throughout the 24 monthly analyses, indicating that there was no significant increase in GBS cases during the study period (January 2021-December 2022).

Figure 1.1 shows critical values, observed data and alpha spending in the 24-month sequential tests for monitoring GBS events after COVID-19 vaccination. The observed empirical information did not reach the signaling threshold up to the end of the surveillance period. The graph shows that the observed relative risk of GBS following COVID-19 vaccination is slightly below 1, the actual alpha spending is also less than the target alpha spending. The observed log-likelihood did not exceed the critical value.

Table 1: Result of GBS using Poisson MaxSPRT

Month	μ_t	Events	Cum. μ_t	Cum. Events	$\widehat{RR}$	LLR	target alpha	actual alpha	CV	Reject H0
1	1.32	1	1.32	1	0.76	0	0	0	*NA*	No
2	1.32	0	2.64	1	0.38	0	0	0	*NA*	No
3	1.32	2	3.96	3	0.76	0	0	0	*NA*	No
4	1.32	1	5.28	4	0.76	0	0.0204	0.0195	3.6265	No
5	1.32	1	6.6	5	0.76	0	0.0228	0.0213	3.4919	No
6	1.32	1	7.92	6	0.76	0	0.025	0.0233	3.4164	No
7	1.32	2	9.24	8	0.87	0	0.027	0.0248	3.4926	No
8	1.32	0	10.56	8	0.76	0	0.0289	0.0261	3.289	No
9	1.32	3	11.88	11	0.93	0	0.0306	0.0293	3.261	No
10	1.32	4	13.2	15	1.14	0.12	0.0323	0.031	3.2087	No
11	1.32	0	14.52	15	1.03	0.01	0.0339	0.0322	3.1606	No
12	1.32	4	15.84	19	1.2	0.3	0.0354	0.035	3.138	No
13	1.32	2	17.16	21	1.22	0.4	0.0368	0.0364	3.0952	No
14	1.32	2	18.48	23	1.24	0.51	0.0382	0.0374	3.0553	No
15	1.32	1	19.8	24	1.21	0.42	0.0395	0.0381	3.0178	No
16	1.32	1	21.12	25	1.18	0.34	0.0408	0.0399	2.9999	No
17	1.32	1	22.44	26	1.16	0.27	0.0421	0.0407	2.9658	No
18	1.32	1	23.76	27	1.14	0.21	0.0433	0.0426	2.9494	No
19	1.32	1	25.08	28	1.12	0.16	0.0445	0.0436	2.9179	No
20	1.32	0	26.4	28	1.06	0.05	0.0456	0.0456	2.9028	No
21	1.32	6	27.72	34	1.23	0.66	0.0468	0.0465	2.8736	No
22	1.32	3	29.04	37	1.27	1	0.0479	0.0471	2.8458	No
24	1.32	0	31.68	38	1.2	0.59	0.05	0.0492	2.8458	No

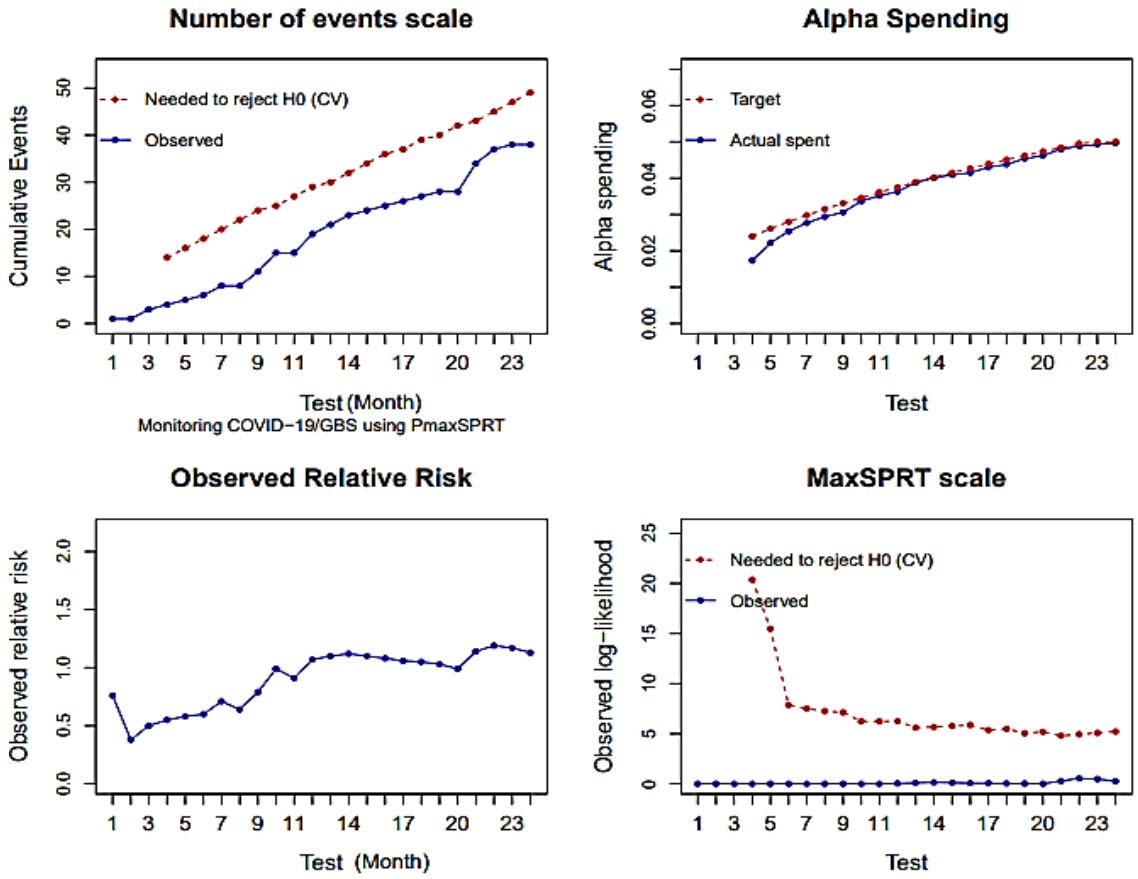

Figure 1: GBS cases following COVID-19 vaccinations using PMaxSPRT.

Table 2: Sequential Monitoring Anaphylaxis following COVID-19 Immunizations

Month	μ_t	Event	Cum μ_t	Cum. Events	$\widehat{RR}$	LLR	target alpha	actual alpha	CV	Reject H_0
1	1.56	2	1.56	2	1.28	0.06	0.0102	0.0054	6	No
2	1.56	1	3.12	3	0.96	0	0.0144	0.0088	9	No
3	1.56	0	4.68	3	0.64	0	0.0177	0.0143	11	No
4	1.56	0	6.24	3	0.48	0	0.0204	0.0202	13	No
5	1.56	1	7.8	4	0.51	0	0.0228	0.022	16	No
6	1.56	3	9.36	7	0.75	0	0.025	0.0244	18	No
7	1.56	1	10.92	8	0.73	0	0.027	0.0268	20	No
8	1.56	3	12.48	11	0.88	0	0.0289	0.0276	23	No
9	1.56	3	14.04	14	1	0	0.0306	0.0306	24	No
10	1.56	4	15.6	18	1.15	0.18	0.0323	0.0312	27	No
11	1.56	5	17.16	23	1.34	0.9	0.0339	0.0321	29	No
12	1.56	8	18.72	31	1.66	3.36	0.0354	0.0348	30	Yes
13	1.56	5	20.28	36	1.78	4.94	NA	NA	NA	Yes
14	1.56	0	21.84	36	1.65	3.83	NA	NA	NA	Yes
15	1.56	7	23.4	43	1.84	6.56	NA	NA	NA	Yes

16	1.56	1	24.96	44	1.76	5.9	NA	NA	NA	Yes
17	1.56	1	26.52	45	1.7	5.31	NA	NA	NA	Yes
18	1.56	0	28.08	45	1.6	4.3	NA	NA	NA	Yes
19	1.56	1	29.64	46	1.55	3.86	NA	NA	NA	Yes
20	1.56	0	31.2	46	1.47	3.06	NA	NA	NA	Yes
21	1.56	6	32.76	52	1.59	4.79	NA	NA	NA	Yes
22	1.56	3	34.32	55	1.6	5.26	NA	NA	NA	Yes
23	1.56	1	35.88	56	1.56	4.81	NA	NA	NA	Yes
24	1.56	0	37.44	56	1.56	3.99	NA	NA	NA	Yes

The critical values (CV) are given in the scale of cumulative events. M = 4, z = 2, cv = 3.15, NA= Not available. The maximum length of surveillance is 37.44 under a power-type alpha spending (ρ = 0.5) with α = 0.05

It has been found that the null hypothesis was rejected in the twelfth month in Table 2, indicating that there was an increase in anaphylaxis cases during the study period. Figure 1.2 shows the observed signaling thresholds in the MaxSPRT scales. Note how irregular the shapes of the thresholds as the testing time evolves. The observed empirical information reached the signaling threshold in the 12th month. This signal occurred when the total amount of information reported a relative risk estimate about 1.7. The actual alpha spending is less than the target alpha; the log-likelihood reached the critical value at the twelve month.

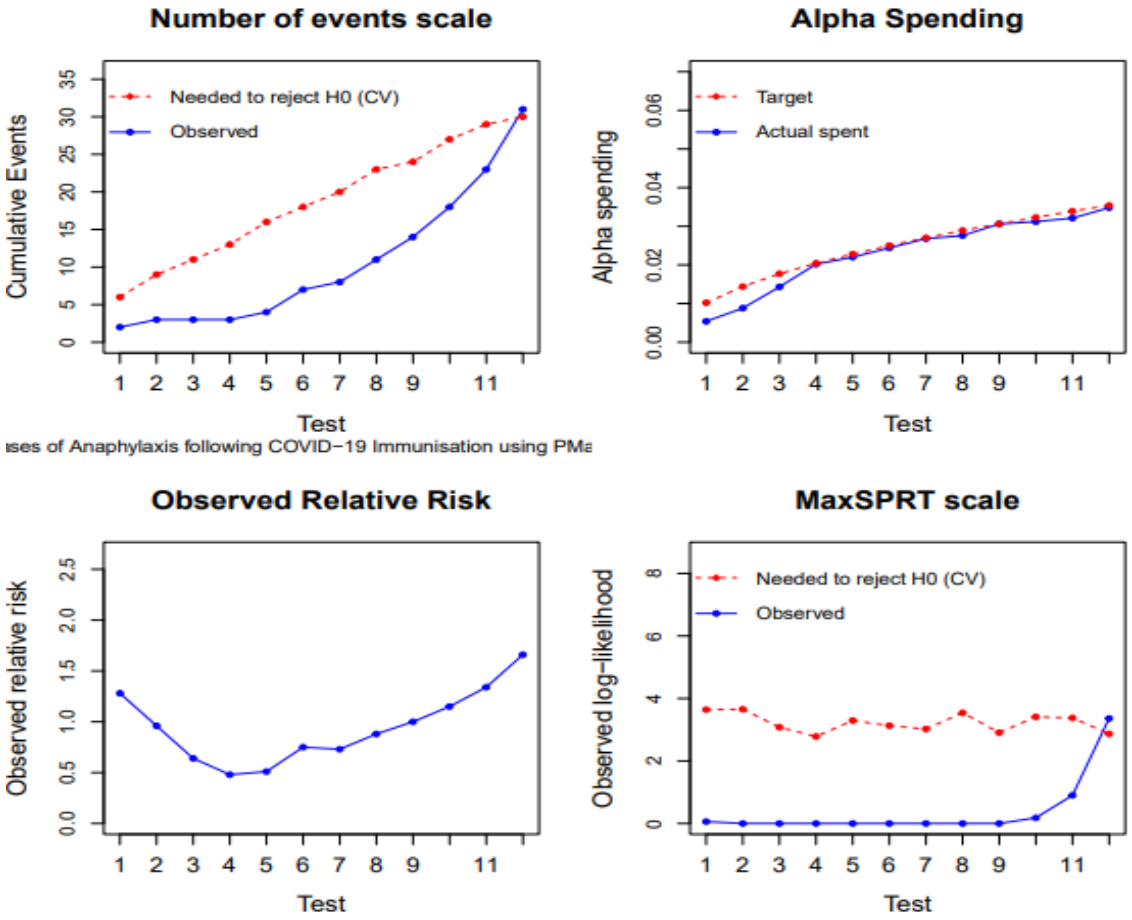

Figure 2: Monthly Sequential monitoring of anaphylaxis using PMaxSPRT

Table 3: Sequential Result of syncope after COVID-19 Immunizations

Month	Cases	Controls	Cum. Cases	Cum. Controls	E[Cases|H0]	RR estimate	LLR	Reject H0
1	1	1	1	1	0.67	2	0.118	No
2	2	0	3	1	1.33	6	1.452	No
3	1	3	4	4	2.67	2	0.471	No
4	6	2	10	6	5.33	3.33	2.834	No
5	6	1	16	7	7.67	4.57	6.282	Yes
6	2	0	18	7	8.33	5.14	7.789	Yes
7	5	1	23	8	10.33	5.75	10.81	Yes
8	5	1	28	9	12.33	6.22	13.883	Yes
9	5	4	33	13	15.33	5.08	14.137	Yes
10	6	0	39	13	17.33	6	18.8755	Yes
11	10	3	49	16	21.67	6.12	24.045	Yes
12	16	9	65	25	30	5.2	28.371	Yes
13	35	3	100	28	42.67	7.14	53.973	Yes
14	14	1	114	29	47.67	7.86	64.892	Yes
15	4	0	118	29	49	8.14	68.394	Yes
16	7	1	125	30	51.67	8.33	73.335	Yes
17	9	0	134	30	54.67	8.93	81.346	Yes
18	3	2	137	32	56.33	8.56	81.473	Yes
19	6	2	143	34	59	8.41	84.292	Yes
20	5	1	148	35	61	8.46	87.475	Yes
21	5	1	153	36	63	8.5	90.658	Yes
22	7	0	160	36	65.33	8.89	96.899	Yes
23	10	7	170	43	71	7.91	97.0612	Yes
24	7	1	177	44	73.67	8.05	101.984	Yes

The BMaxSPRT method in Table 3 generated a signal in the fifth month for syncope; the null hypothesis was rejected after the critical value falls below the log-likelihood ratio (LLR). This indicates and association between syncope and COVID-19 vaccine. However, association detected by maximized-SPRT does not implies causation, further epidemiologic studies are needed to validates the association.

Table 4: Results of Seizures Using PMaxSPRT and BMaxSPRT

	Cases/events	RR Estimate	log likelihood	Critical Value	Month
BMaxSPRT	15	4.4	6.348	4.852	8
PMaxSPRT	35	1.46	3.2	3.08	14

We were able to replicate a known signal for febrile seizures following COVID-19 vaccine based on a 2-year surveillance in Table 4. We applied both approaches and detected a signal when the LLR of 6.348 exceeded the CV of 4.582 for BMaxSPRT. Statistical signal was later identified with PMaxSPRT identified after LLR value of 3.2 exceeded a CV value of 3.08. The BMaxSPRT has been the most suitable methods to study common adverse events. The method detected signals very early, the first signal detected by the method occurred in August 2021, while the PMaxSPRT generated signal in the fourteenth month which was six month later. The PMaxSPRT is the suitable for modelling rare events, it detects a modest elevation in risk, and the method is more powerful than BMaxSPRT. The

difference between the two lies in their statistical approaches, BMaxSPRT compares the number of events between time periods within individuals. On the other hand, PMaxSPRT is based on observed and expected number of events. This research underscores the importance of rigorous safety surveillance during mass vaccination campaigns. The application of Poisson and Binomial-based MaxSPRT methods allows for efficient signal detection, particularly for rare adverse events. With these findings, we add to the safety profile established in pre-licensure clinical trials.

3.2 Discussions

Sequential analysis of GBS cases over a 24-month period using PMaxSPRT was conducted as shown in Table 1. It has been found that the null hypothesis was not rejected throughout the 24 monthly analyses, indicating that there was no significant increase in GBS cases during the study period (January 2021-December 2022). The finding of no statistical signal is consistent with previous studies that have reported no significant increase in GBS cases following COVID-19 vaccination (Llord *et al*., 2022). Gee *et al*. (2011) found no significant increase in GBS cases following administration of 600,558 doses of HPV4. Donahue *et al.* (2019), also reported no significant increase in GBS cases following 9-valent human papillomavirus vaccine (9vHPV). Overall, our findings suggest that COVID-19 vaccine is not associated with a significant increase in GBS cases. However, further research is needed to confirm these findings and to identify any potential risk factors for GBS. In Table 2. It has been found that the null hypothesis was rejected in the 24 monthly analyses, indicating that there was an increase of anaphylaxis cases during the study period. Investigation for an increased risk of anaphylaxis 6 weeks after COVID-19 vaccinations conducted is consistent with published literature in which anaphylaxis met the statistical threshold for a signal in the all-dose analysis following COVID-19 vaccination with RR = 10.86 andT = 39 (Llord *et al*., 2022).

The BMaxSPRT method in Table 3 generated a signal in the fifth month for syncope; the null hypothesis was rejected after the critical value falls below the LLR. At least 5 events was required to occur before a statistical signal could be generated, this was to avoid spurious signaling that would otherwise have been possible due to a chance early occur and optimize power. Our findings agree with that of (Tequare *et al*., 2021), in which common adverse events following COVID-19 immunization are found to be related to the vaccine. Donahue *et al.* (2019) also reported that there was a signal for syncope in multiple subgroups of women 18 to 26 years old; the RRs were ≤ 2.0 in each of these subgroups. Known signal for febrile seizures following COVID-19 vaccine based on a 2-year surveillance was replicated in Table 4. Both approaches detected signals when the LLR of 6.348 exceeded the CV of 4.582 for BMaxSPRT. Statistical signal was later identified with PMaxSPRT identified after LLR value of 3.2 exceeded a CV value of 3.08. This finding is consistent with the previous study of seizures following MMR based a one-year surveillance period by Leite *et al*. (2017), in their study, signal was identified with PMaxSPRT after 3 months of surveillance, when a minimum events of 2 events was stipulated.

4.0. Conclusion

In the study of vaccine surveillance titled "Early Detection of Safety Signal for COVID-19 Vaccine Safety Surveillance," this research focused on assessing the safety of COVID-19 vaccines with a particular emphasis on potential adverse events. The thesis proposed that advanced statistical methods could effectively identify any associations between the COVID-19 vaccine and certain medical conditions. The findings concluded that there is no association between COVID-19 vaccination and Guillain-Barré Syndrome (GBS). However, a slight increase in the risk of anaphylaxis, seizure, and syncope following COVID-19 vaccination was identified. The simultaneous application of Poisson and Binomial Maximized Sequential Probability Ratio Testing (SPRT) proved to be a suitable approach for studying vaccine safety concerns due to the complementary strengths of these two methodologies. The significance of these results lies in their implications for public health policies and the ongoing monitoring of vaccine safety. Ensuring the safety and efficacy of COVID-19 vaccination programs is paramount, and these findings support the need for continuous surveillance. Further research is essential to uncover any potential associations or emerging risk factors over time, thereby contributing to the overall understanding and confidence in COVID-19 vaccines.

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