

Syndromic Surveillance of Post-vaccination Adverse Events using SPRT: a Retrospective Analysis

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Charts derived from the sequential probability ratio test (SPRT) have been widely used in industry to monitor process performance.

The SPRT is used for situation where the monitoring is continuous and items can be inspected 1 by 1.

Studies have shown that charts based on the SPRT will signal an “out of control” process earlier than either the Shewhart p-charts or the CUSUM chart.

Recently there has been increased attention paid to the use of the CUSUM and SPRT charts in a medical context.

- Monitoring surgical failures (Spiegelhalter, Grigg).
- Monitoring in syndromic data sets for aberrations (Hutwagner).

We propose using the SPRT to monitor for an increase/decrease in probability of an adverse event following the introduction of a new vaccine. The SPRT will use data from the Vaccine Safety Datalink (VSD) in a rapid cycle format.

To develop and test methods for conducting this real time surveillance, we used retrospective data from the VSD to examine:

- The switch from DTP to DTaP.
- The introduction of Rotavirus vaccine.

The Vaccine Safety Datalink

- Created in 1991 with 4 participating HMOs to provide an infrastructure to study important topics in vaccine safety
- Largest such collaborative in the United States
- Coordinated by the Centers for Disease Control and Prevention
- Currently includes vaccination, inpatient and outpatient data from 8 participating HMOs
- Covers over 4% of all children < 18 years old in the United States

The SPRT Chart's Hypotheses

- To construct a SPRT chart a null and alternative hypothesis must be specifically specified in the format:

$$H_0 : p = p_0$$

$$H_1 : p = p_1$$

- The hypotheses refers to the probability of an event following vaccination with the newly introduced vaccine.
- SPRT tests generally test one sided hypotheses.

Specifying the hypotheses.

- The null hypothesis would be that the probability has not changed from baseline.
- The alternative hypothesis would express the effect size that is important to detect. It can be expressed as:
 - A proportionate increase or decrease from baseline.
 - A risk ratio or odds ratio.
- For example, we could write the following hypotheses to detect a 40% reduction:

$$H_0 : p = p_0$$

$$H_1 : p = .6 * p_0$$

The Switch from DTP to DTaP.

- Seizures, Fevers, and Other Neurological Events.
- Children < 24 months old.
- 0-3 days post-vaccination.
- Compare proportion of times that a given event followed a vaccination visit that included DTP to the proportion of times that the event followed a vaccination visit that included DTaP.
- Monitor for a 40% decrease in probability of these events.

Calculating the Weekly Chart Entry

- We are accumulating both vaccinations and events by study week to do this analysis.
- For each study week (t), we calculate a statistic (X_t).
- The pair (t, X_t) is plotted on the SPRT chart.

$$X_t = X_{t-1} + W_t$$

$$X_0 = 0$$

The way we calculate W_t , the weekly contribution to the SPRT chart, depends on whether we are adjusting for possible confounders.

Unadjusted SPRT – The Data

Without adjustment, our data would be simply a weekly count of the number of vaccinations and the number of events following these vaccinations.

Week (t)	# Events	# Vaccs
1	0	2000
2	1	8000
3	0	4000

Calculating W_t for Study Week t

$$W_t = \log \left(\frac{L_{1t}}{L_{0t}} \right)$$

- The numerator is the likelihood equation under the alternative hypothesis.
- The denominator is the likelihood equation under the null hypothesis.
- Large values of W_t favor the alternative hypothesis.

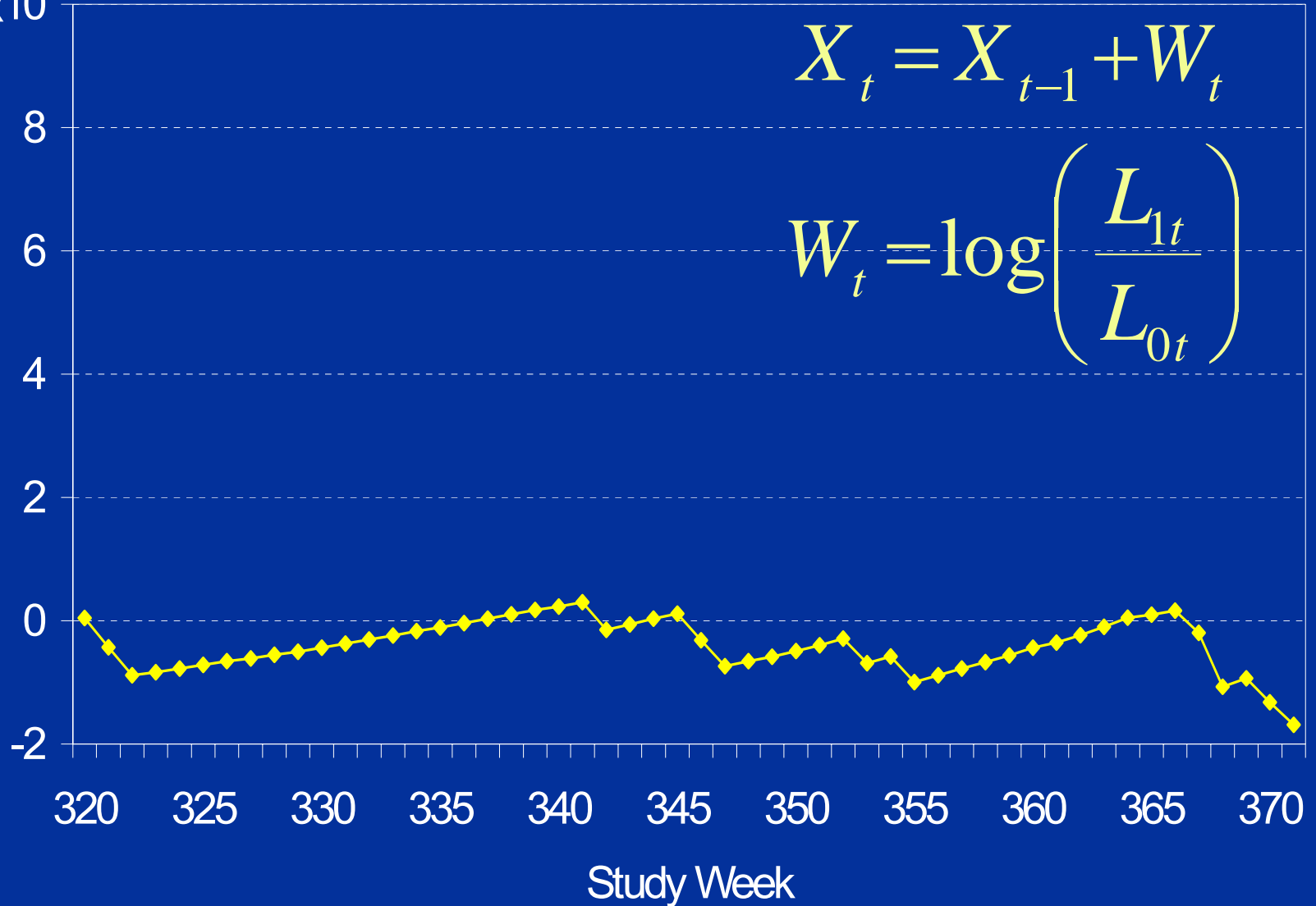
Calculating W_t for Study Week t

- Since we are using grouped data and looking at a proportion, we will be using the binomial distribution to obtain W_t .
- The weighted log likelihood ratio X_t is therefore a function of exact binomial distributions .

$$W_t = \log \left(\frac{\binom{vaccs}{events} p_1^{events} * (1 - p_1)^{vaccs - events}}{\binom{vaccs}{events} p_0^{events} * (1 - p_0)^{vaccs - events}} \right)$$

Sample SPRT Chart

Log LR10



Testing the Null Hypothesis

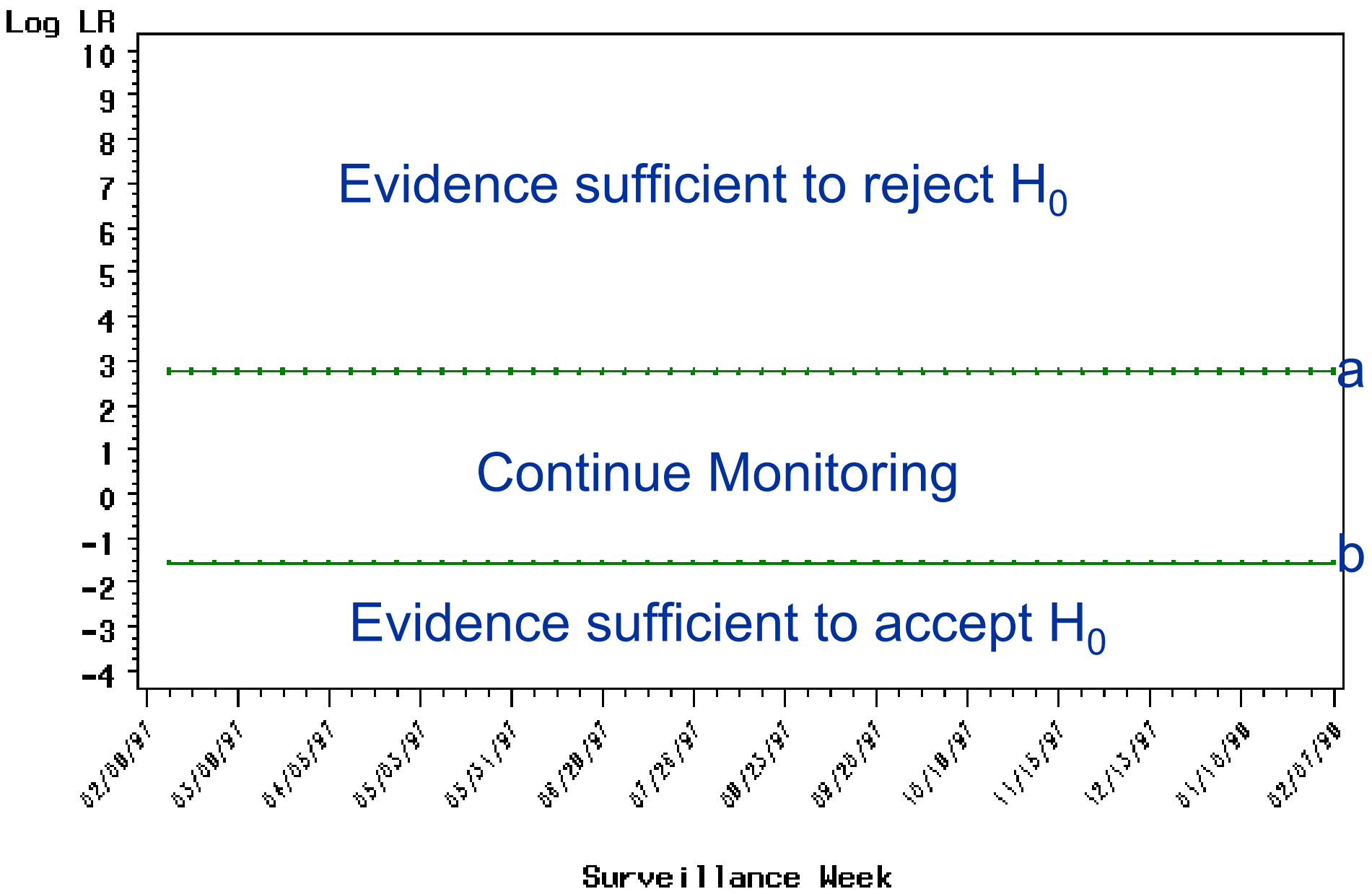
To decide between the null and alternative hypotheses, the SPRT chart sets up two barriers a and b such that:

$b < X_t < a$ Continue monitoring

$X_t \geq a$ Accumulated sufficient information to reject H_0

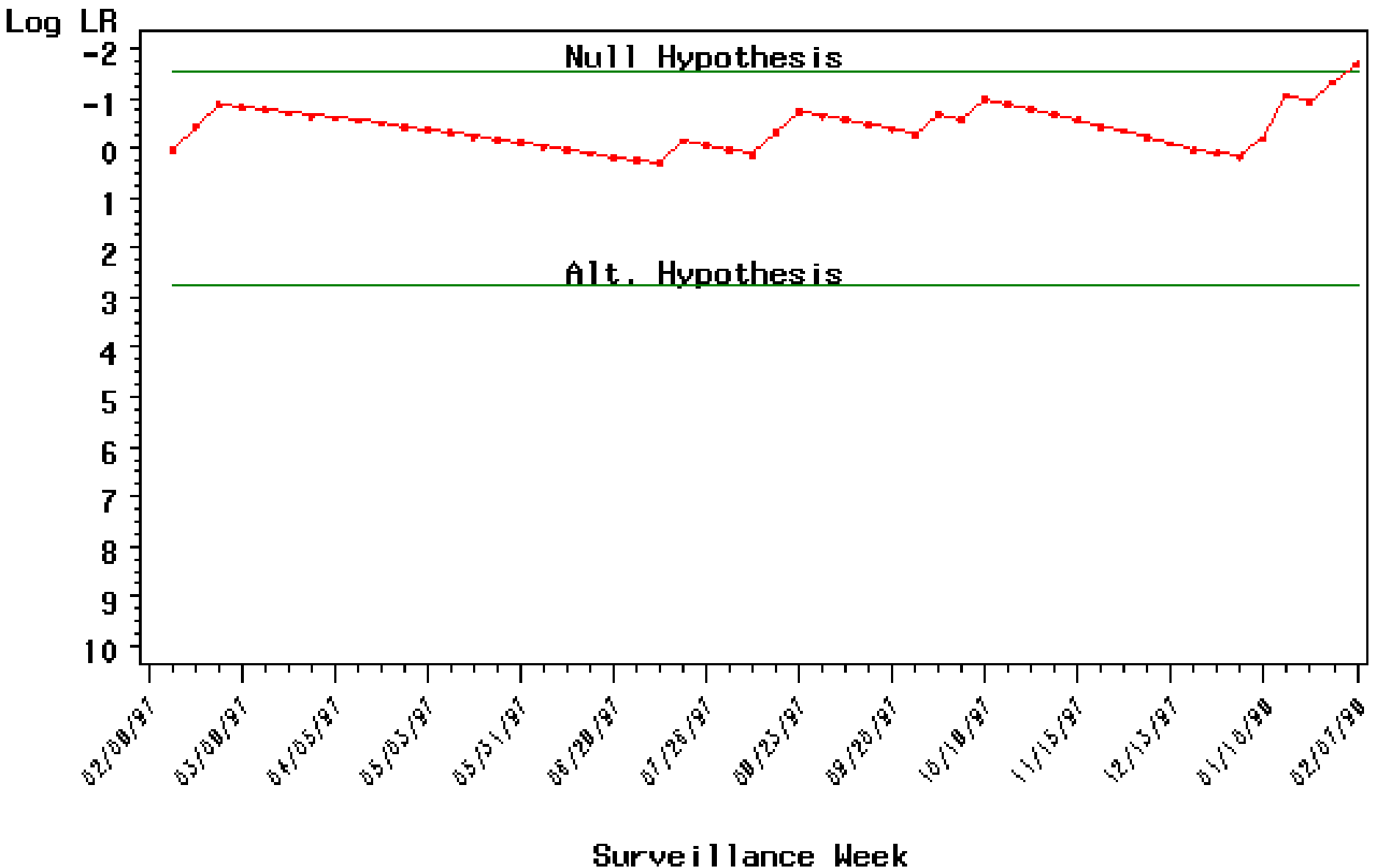
$X_t \leq b$ Accumulated sufficient information to accept H_0

Barriers for SPRT



Seizures – 40% Decrease from DTP to DTaP

0-3 Days Post-vaccination



Calculating the Barriers

We calculate a and b as follows:

$$a = \log\left(\frac{\beta^*}{1 - \alpha^*}\right)$$

$$b = \log\left(\frac{1 - \beta^*}{\alpha^*}\right)$$

The Parameters α^* and β^*

- Under the special circumstance when monitoring is truly continuous and not conducted at discrete time intervals, α^* and β^* are the Type I (α) and Type II (β) errors of the test H_0 versus H_1 .
- When W_t is small, Type I and Type II errors are very close to the specified α^* and β^* .

- With discrete monitoring:

$$\beta \leq \beta^*$$

$$\alpha \leq \alpha^*$$

- The error level is for to the entire process, not for each specific week's view of the data.

Steps in DTP/DTaP Seizure Study

- Calculate p_0 , the probability of a seizure within 3 days following vaccination with DTP.
 - Use a time when the process is considered to be under control. Study weeks 210 – 313 (1995-1996).
 - $p_0 = .000188$

Steps in DTP/DTaP Seizure Study

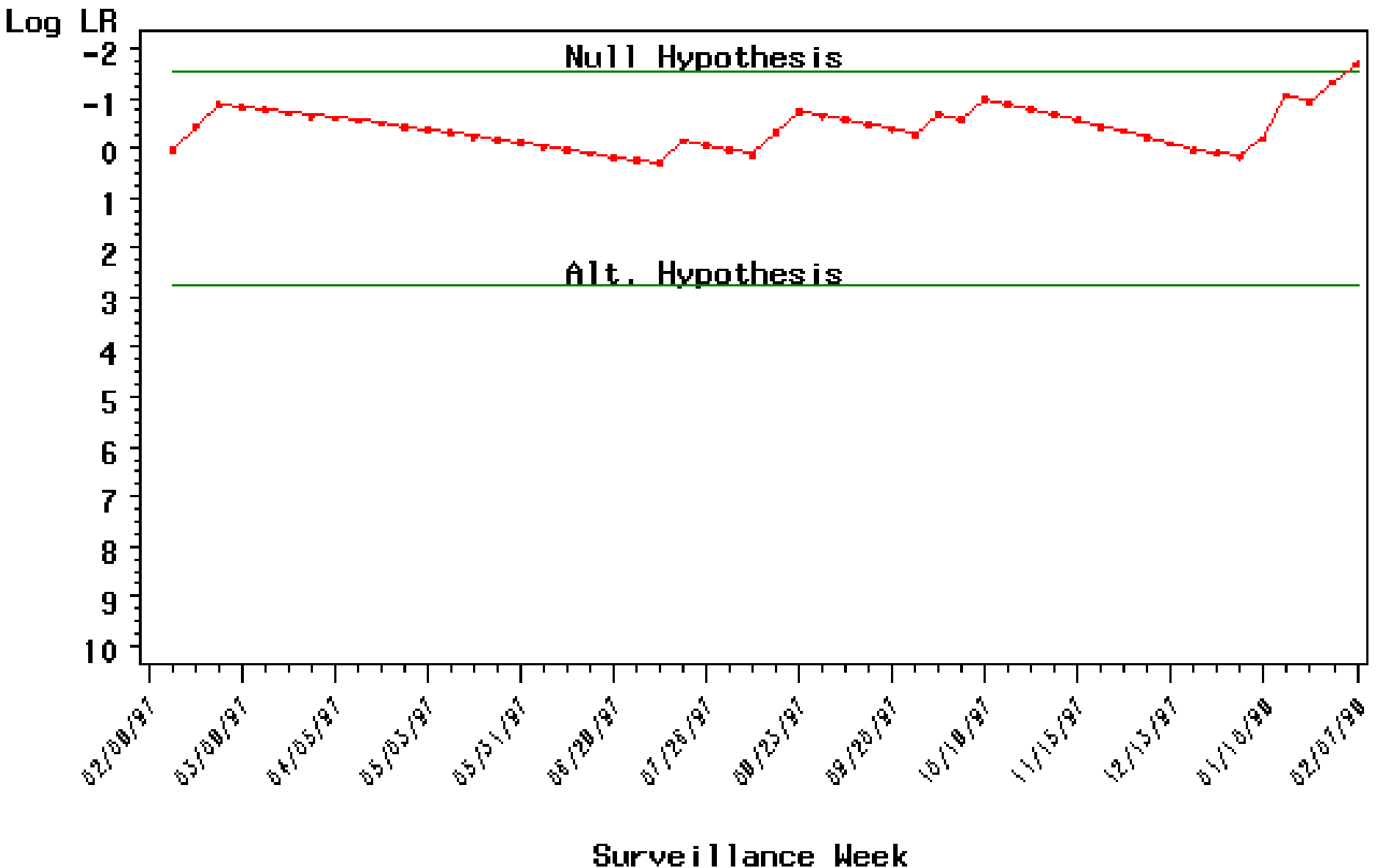
- Set up the SPRT chart to monitor for possible reduction in seizure probability following the switch to DTaP.
 - Determine the absorbing barriers a and b .
 - Determine the alternative hypothesis. For example, based on the evidence from clinical trials, we hypothesized that p is reduced by 40% upon introduction of DTaP.
 - Begin monitoring with study week 320 (2/8/97) and continue for 1 year. The SPRT is testing the following hypotheses:

$$H_0: p = .000188$$

$$H_1: p = .000113$$

Seizures – 40% Decrease from DTP to DTaP

0-3 Days Post-vaccination



Risk-Adjusted SPRT

- The situation becomes more complicated when we control for possible confounders.
- Possible confounder include such factors as HMO, age, calendar time, season.
- When doing risk adjustment, each strata formed by the combination of risk factors will have its own baseline probability of an adverse event (p_{oj}).

Formulas for Risk-adjusted SPRT

- When adjusting for potential confounders, the formula for W_t changes as the likelihood equations allows the p_0 and p_1 in the various strata (j) to differ based on the covariates.

$$W_t = \log \left(\frac{\prod_j p_{1j}^{events_j} * (1 - p_{1j})^{vaccs_j - events_j}}{\prod_j p_{0j}^{events_j} * (1 - p_{0j})^{vaccs_j - events_j}} \right)$$

How are the p_{0j} obtained?

- p_{0j} are obtained by conducting a logistic regression on the baseline data.
- Based on this regression, probabilities of an event occurring are estimated for both the baseline and surveillance data.
- Each combination of the covariates will have a unique p_{0j} .

Events/Vaccs = week age site

Example of Data Used to Monitor a New Vaccine's Adverse Events when Risk-Adjusting

Week(t)	#Events	#Vaccs	Site	Agegroup	p_{oj}
1	20	1000	A	0-5 mon	.0001
1	19	670	A	6-12 mon	.0030
1	34	1030	B	0-5 mon	.0005
1	10	500	B	6-12 mon	.0010
2	10	750	A	0-5 mon	.0001

Monitor the New Process

- Once we have the predicted probabilities obtained from the baseline data, we begin to monitor the new process using the formulas for W_t and X_t .
- Only the data from the new process (vaccine) is used to test the hypothesis.
- The alternative hypothesis is specified and the p_{1j} are calculated assuming the same effect size in each strata.

$$H_0: p_j = p_{0j}$$

$$H_1: p_j = p_{1j} = .6 * p_{0j}$$

Calculating Weekly Contribution to SPRT

- The values of p_{0j} and p_{1j} for each strata are substituted into the formulas to calculate the weeks contribution to the log likelihood ratio.

$$W_t = \log \left(\frac{\prod_j p_{1j}^{events_j} * (1 - p_{1j})^{vaccs_j - events_j}}{\prod_j p_{0j}^{events_j} * (1 - p_{0j})^{vaccs_j - events_j}} \right)$$

$$X_t = X_{t-1} + W_t$$

$$X_0 = 0$$

DTP/DTaP Seizure Study

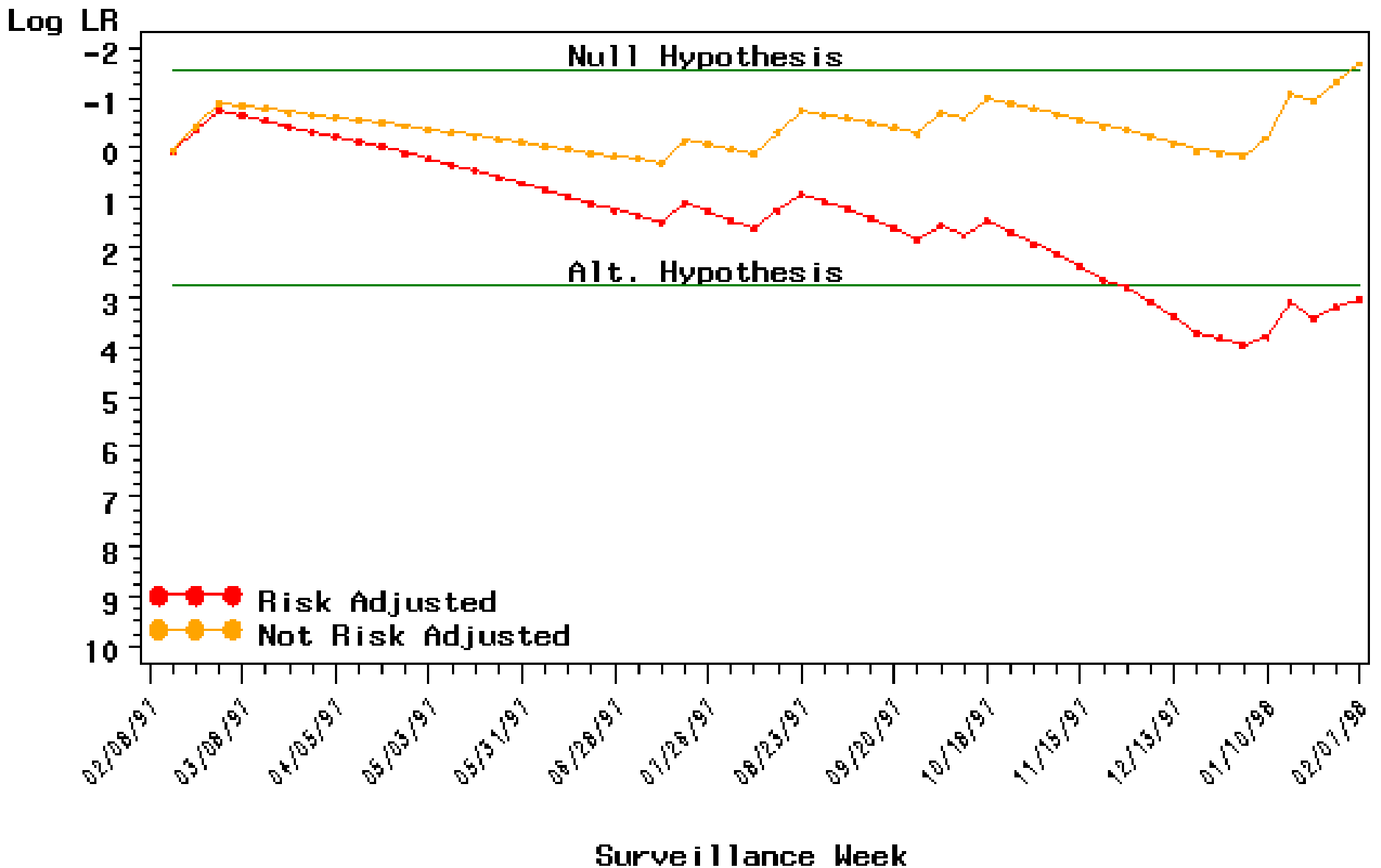
- Logistic Regression to determine p_{oj}
 - Study Week 210 – 313 (1995-1996)
 - Seizures/#DTP = time + age group + site
 - Time was continuous (study week -209)

DTP/DTaP Seizure Study

- Surveillance for a 40% reduction in seizure probability.
 - Set up the absorbing barriers.
 - Study Week 320 – 371 (1 year following common use of DTaP)
 - Calculate p_{1j} as $p_{1j} = .6 p_{0j}$
 - Create the SPRT to test the hypothesis that there was a 40% reduction in the probability of a seizure following vaccination with DTaP.

Seizures – 40% Decrease from DTP to DTaP

0-3 Days Post-vaccination



Advantages of SPRT Charts for Monitoring Vaccine Safety

- Uses the exact binomial distribution rather than normal approximation. (For rare events, the normality assumption generally does not apply.)
- Is a sequential testing method where Type I and Type II errors apply to the entire monitoring process rather than to each week's view of the data.
- Allows for risk-adjustment based on possible confounders.
- Can be easily implemented in SAS.

References

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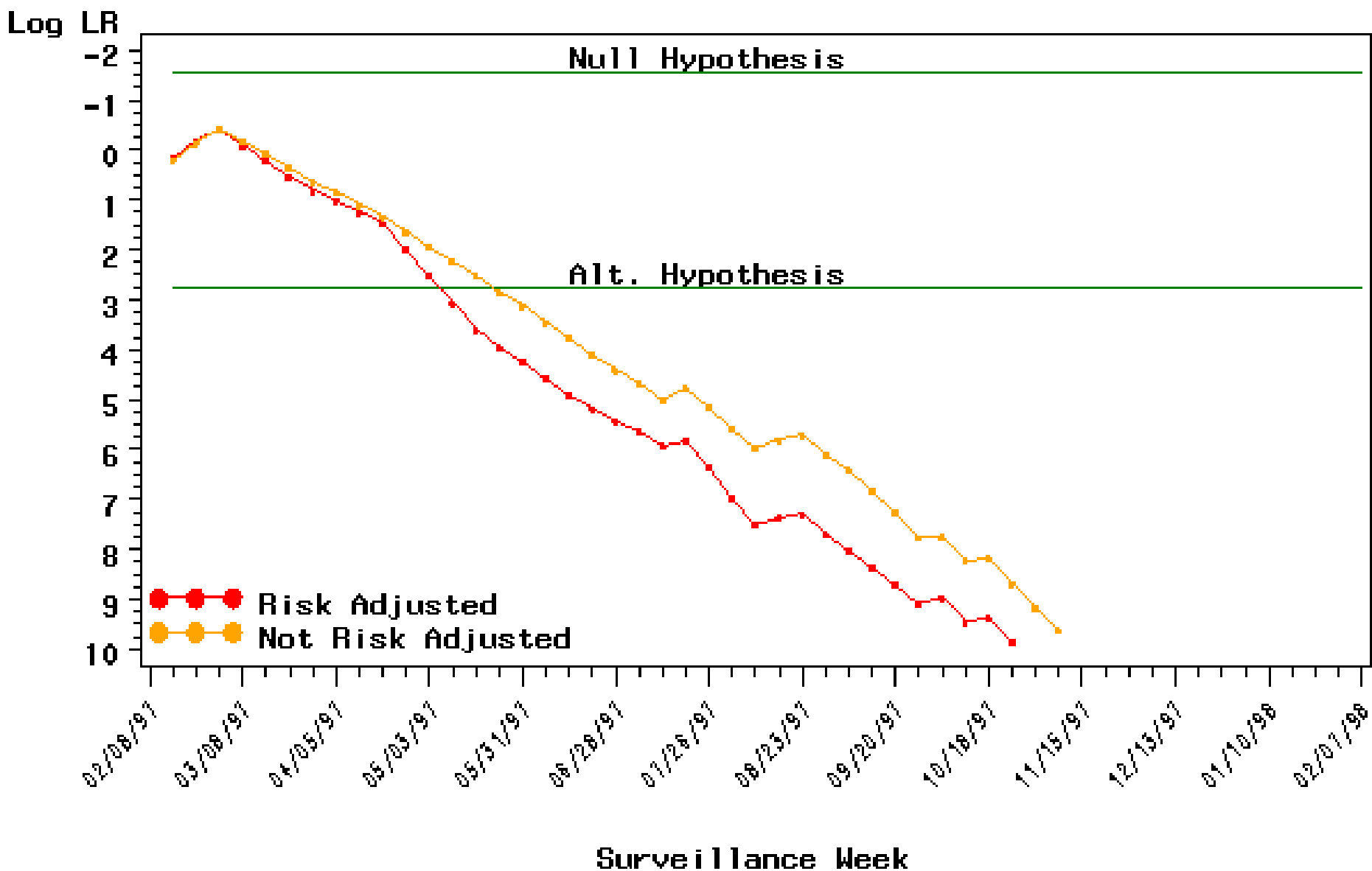
+ SPRT

Lori Hutwagner
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Rapid Cycle Risk-adjusted SPRT Results
DTP/DTaP and Fever, Seizure, Other Neuro

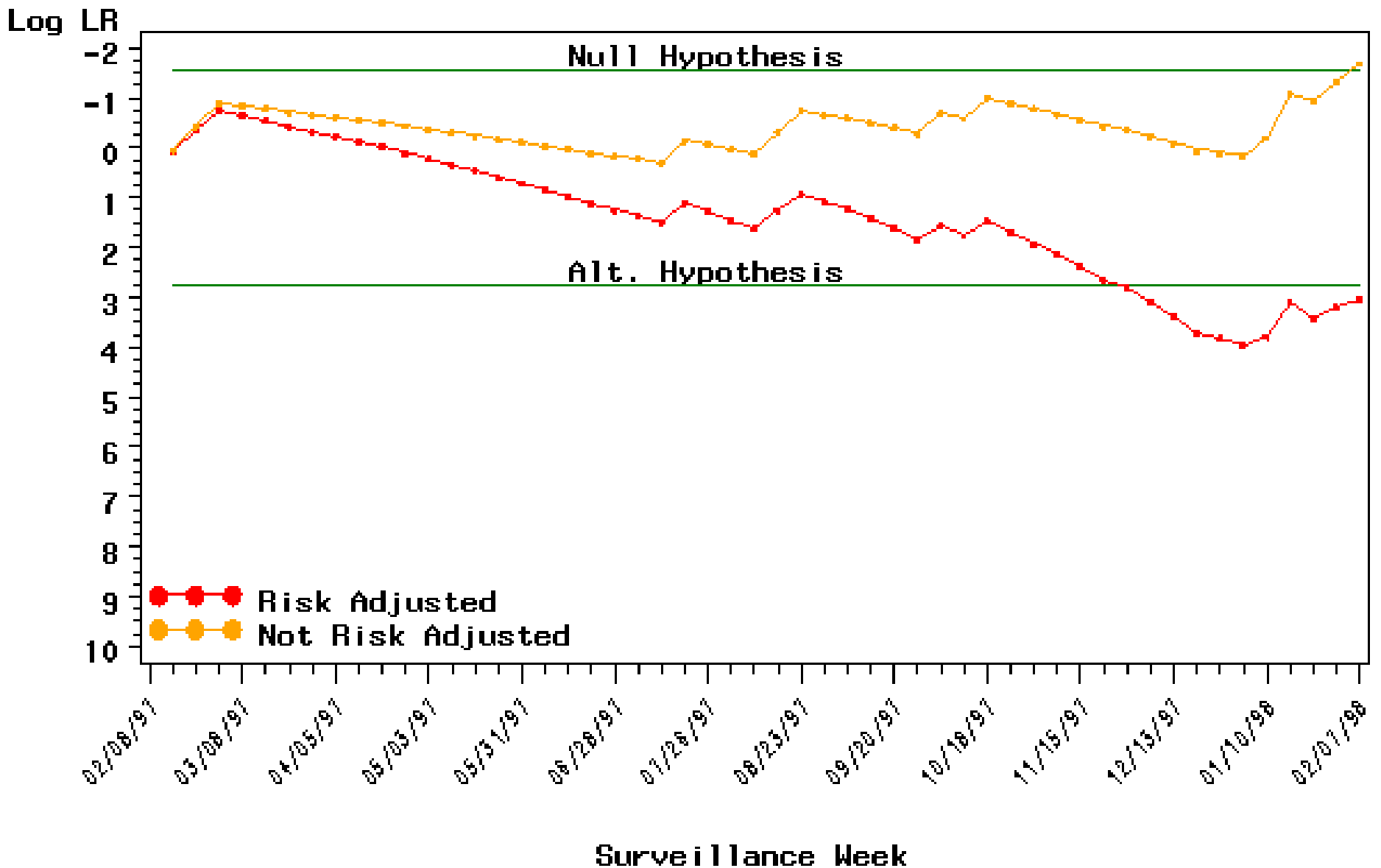
Fever Events – 40% Decrease from DTP to DTaP

0-3 Days Post-vaccination



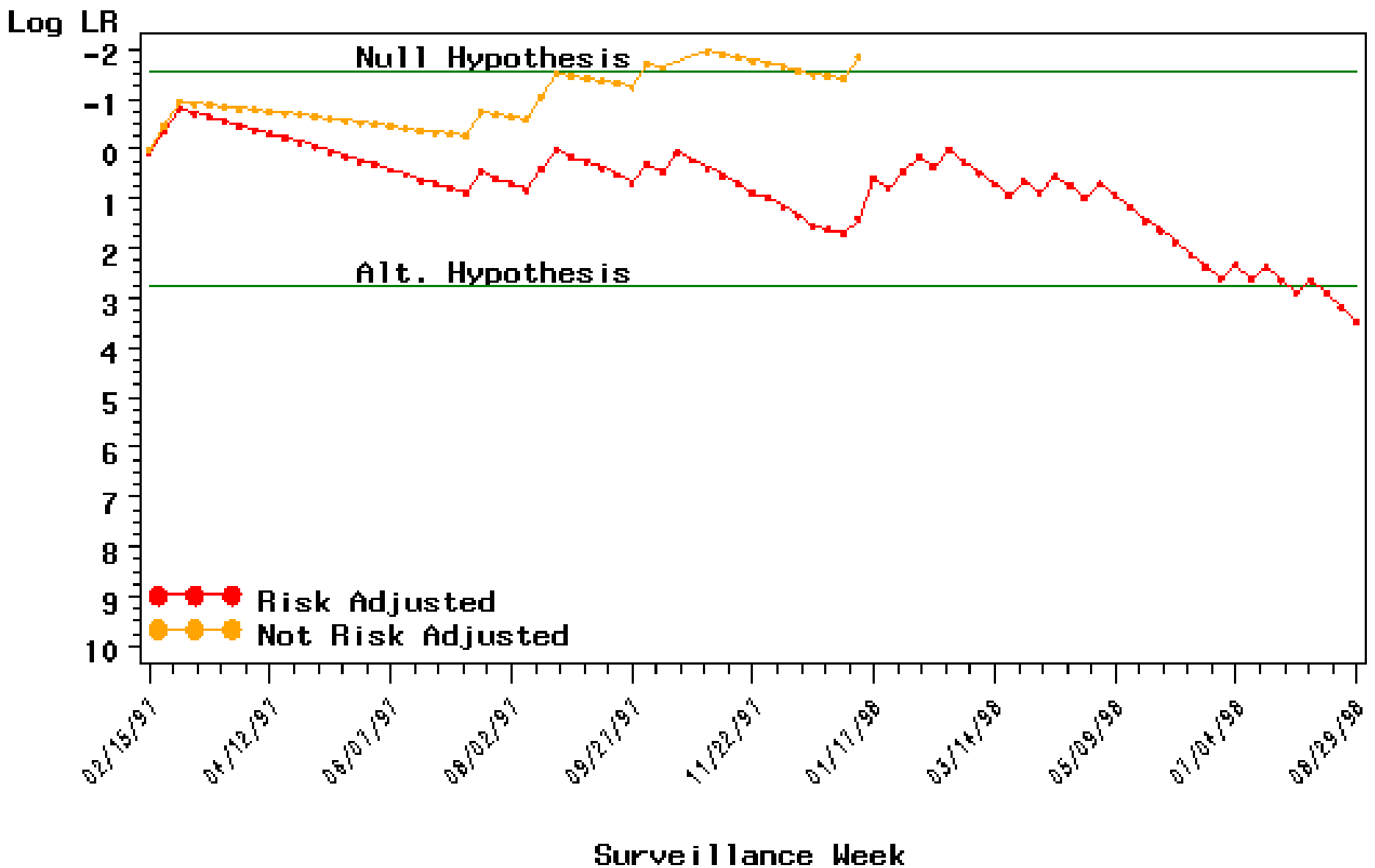
Seizures – 40% Decrease from DTP to DTaP

0-3 Days Post-vaccination



Neurological Events – 40% Decrease from DTP to DTaP

0-3 Days Post-vaccination



Rapid Cycle SPRT Results Intussusception and Rotavirus Vaccine

Intussusception — 10 Fold Increase Following Rotavirus Vaccine

(0-30 Days Post vaccination, < 8 mon old)

