Centers for Disease Control and Prevention
Epidemiology Program Office
Case Studies in Applied Epidemiology
No. 831-704

Tampons and Toxic Shock Syndrome

Student's Guide

Learning Objectives
After completing this case study, the participant should be able to:

☐ Describe the concepts, applications, and limitations of matching in case-control studies;

☐ Analyze matched case-control data; and

☐ Discuss the issues involved in appropriate selection of controls in case-control studies.

This case study was developed in 1983 by Richard Dicker and Ruth Berkelman. It has been revised and edited over the years by Richard Dicker, with input from the EIS Summer Course instructors.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

PART I

In 1979, three cases of an unusual illness were reported to the Wisconsin State Health Department. The three cases, all of which occurred in women, were characterized by fever, low blood pressure, diffuse rash, skin peeling, and impairment of multiple organ systems. This clinical presentation was reminiscent of an illness described a year earlier by Todd et al. and given the name Toxic Shock Syndrome (TSS). Todd's case series consisted of four girls and three boys 8 to 17 years old, five of whom had focal *Staphylococcus aureus* infections.

As a result of the case reports, Wisconsin and Minnesota established TSS surveillance systems within their states. By January of 1980, the two states had identified a total of 12 cases, all in women. Eleven of the 12 women had been menstruating at the onset of illness, and, anecdotally, "most" had been using tampons during the corresponding menstrual period. Soon thereafter, CDC was notified. In February, Utah established an active surveillance system.

During the spring of 1980, reports of TSS continued to trickle into CDC, mostly from Wisconsin, Minnesota, and Utah. The lead article of the May 23, 1980 issue of the *Morbidity and Mortality Weekly Report (MMWR)* described the first 55 reported cases of TSS. Of 40 patients in whom a menstrual history was obtained, 38 (95%) had onset of illness within 5 days following onset of menses. The case-fatality rate was 7/55, or 13%. In contrast, the case-fatality rate was 3.2% in Wisconsin, where surveillance had been very active.

Extensive publicity followed this report, and CDC began to receive reports of TSS from other areas of the country.

Question 1: Why might the Wisconsin case-fatality rate have been so much lower than the national case-fatality rate?

In mid-June, CDC conducted its first TSS case-control study (CDC-1). Published in the *MMWR* of June 27, the study of 52 female cases and 52 age- and sex-matched friend controls found a statistically significant association between tampon use and TSS. The report cited two independent preliminary studies from Wisconsin (31 cases) and Utah (12 cases). The Wisconsin study also found a statistically significant association between tampons and TSS, but the Utah study failed to find a statistically significant association.

The article listed p-values, but not odds ratios or other measures of association. Neither the CDC-1 study nor the Wisconsin study found a statistically significant association between any specific brand of tampons and TSS.

The data from the three studies, limited to menstruating women, are summarized in Tables 1, 2, and 3.

Table 1

		Cases	Controls	
CDC-1*	Tampon users	50	43	Reported p = 0.02
	Non-users	0	7	

Table 2

		Cases	Controls	
WISCONSIN	Tampon users	30	71	Reported p = 0.014
	Non-users	1	22	

Table 3

		Cases	Controls	
UTAH	Tampon users	12	32	p not reported, but p = 0.20
	Non-users	0	8	

* excludes 2 non-menstrual cases and their controls

Question 2: From these data, does it appear that TSS is associated with tampon use? Do you consider the Utah study to be consistent or inconsistent with the other two studies?

As mentioned above, the CDC-1 study was a matched-pair case-control study. When the CDC-1 study was published in a peer-reviewed journal, the authors displayed and analyzed the data in matched-pair fashion. Their analysis of continual tampon use during the index menstrual period is shown in Table 4.

Table 4. Continual Tampon Use During Index Menstrual Period, CDC Study (#1) of Toxic Shock Syndrome, 1980

		CONTROLS		
		Exposed	Unexposed	
CASES	Exposed	e=33	f=16	Odds ratio (OR) = f/g
	Unexposed	g=1	h=2	$X^2 = (f-g)^2 / (f+g)$

Question 3: Comment on the difference between this 2-by-2 table (Table 4) and the previous ones.

Question 4a: How many cases used tampons continually?
Question 4b: How many cases did not use tampons continually?
Question 4c: How many controls used tampons continually?
Question 4d: How many controls did not use tampons continually?

Question 5: Calculate the odds ratio and chi-square.

Question 6: Which 2-by-2 table format is appropriate for this study?

In the matched analysis, the 95% confidence limits for this association were 2.1 and 120.6.

Question 7: Describe and interpret the odds ratio and confidence interval from the matched analysis.

Question 8: Have you been given enough information to decide whether the association is real or artifactual?

National publicity followed the June 27 report and continued almost daily throughout the summer of 1980. Though not documented by the studies cited, the lay press speculated that the then-new, highly absorbent tampons such as Rely brand might be responsible for cases of TSS.

By September 5, 1980, CDC had received reports of 272 cases. At that time, CDC launched a second case-control study (CDC-2) to test the hypothesis that one or more brands of tampons might be more strongly associated with TSS than were other brands. The case group was to consist of the 50 surviving females with onset of illness during July-August, 1980.

Question 9: What are some of the potential biases introduced by the MMWR reports and the intense publicity?

Assume it is September 1980 and you have been asked to test the hypothesis that women of menstrual age (say, 12-49 years) who use hypothetical Brand X tampons during menses are at greater risk of TSS than are other women.

Question 10: Assuming that you would conduct a case-control study using the 50 women with onset of TSS in July and August as your case group, who might you include in your control group? What are some of the possible sources for these controls?

Because age frequently is a confounding variable, the following (fictitious) marketing research data might help you in determining whether age is a confounder of the relationship between TSS and Brand X tampon.

(No such marketing data on Rely was available to investigators in 1980.)

Tables 6 and 7 indicate the distribution of women who used only one brand of tampon at the time of the study.

Table 6. Distribution of hypothetical-Brand-X-loyal tampon users and TSS cases among women age 12-49 years, United States, 1980

Brand	# of Users	% of All Users	# TSS Cases	Risk of TSS per 100,000 users
Brand X	4,900,000	14%	452	9.22
All others	30,100,000	86%	386	1.28
	35,000,000	100%	838	

Note that Brand X holds 14% of the brand-loyal tampon-user market. However, the product is much more popular among young women than among older women, as shown in Table 7.

Table 7. Distribution of hypothetical-Brand-X-Loyal tampon users and TSS cases among women age 12-49 years, by age, United States, 1980

Women aged 12-29 years

Brand	# of Users	% of All Users	# TSS Cases	Risk of TSS per 100,000 users
Brand X	4,750,000	(24%)	447	9.41
All others	15,250,000	(76%)	287	1.88
	20,000,000	(100%)	734	

Women aged 30-49 years

Brand	# of Users	% of All Users	# TSS Cases	Risk of TSS per 100,000 users
Brand X	150,000	(1%)	5	3.33
All others	14,850,000	(99%)	99	0.67
	15,000,000	(100%)	104	

Question 11: Calculate risk ratios for the data in Tables 6 and 7. Is confounding present? How can you tell? What can you do about it?

Question 12: What are the advantages and disadvantages of matching?

Question 13: As in Question 10, if you were designing a case-control study using the 50 women with onset of TSS in July and August as your case group, would you match? Why or why not? On which characteristics would you match? What type of matching would you use?

For the CDC-2 study, eligible cases had to have been female TSS patients with onset of illness during July-August, 1980, who were reported to CDC by September 5, 1980, who survived their illness, and who met the CDC definition for TSS. Fifty cases met these eligibility criteria.

For controls, the cases were asked to provide the names of three female friends or acquaintances of the same age (within 3 years) who lived in the same geographic area. The investigators selected three controls rather than one for each case to increase their ability to detect an association between TSS and use of a particular brand of tampon, assuming that such an association existed.

Question 14: Do you agree with the CDC-2 investigators' decision to use friends or acquaintances as controls?

One of the subanalyses of the CDC-2 study focused on the use of Rely brand tampons. This subanalysis excluded cases and controls who did not use tampons at all or who used more than one brand of tampon during the index menstrual period. As a result of these exclusions, in this subanalysis some cases were matched to three controls and some were matched to only two controls. The data are shown in Tables 8a and 8b.

Note to Students: If little time is remaining for the case study, your instructor may elect to skip this part and resume with the text above Question #15.

Table 8a. Exclusive use of Rely brand tampons by (TSS) cases and controls, limited to Quadruplets (1 case, 3 controls) who used tampons, CDC-2 Study, 1980

		# controls using Rely				
		3 of 3	2 of 3	1 of 3	0 of 3	
Cases using Rely?	Yes	1	1	5	4	11
	No	0	1	1	1	3
		1	2	6	5	14 quadruplets

OR = 7.7 (1.4, 42.1)
chi-square = 9.59
chi = 3.09
2-tailed p = 0.002

Table 8b. Exclusive use of Rely brand tampons by (TSS) cases and controls, limited to Triplets (1 case, 2 controls) who used tampons, CDC-2 Study, 1980

		# controls using Rely			
		2 of 2	1 of 2	0 of 2	
Cases using Rely?	Yes	3	3	7	13
	No	0	3	4	7
		3	6	11	20 triplets

OR = ___ (___, ___)
chi-square = 7.54
chi = 2.75
2-tailed p = 0.006

A formula for calculating an odds ratio with c controls per case is:

$$OR = \frac{\text{\# unexposed controls matched with exposed cases}}{\text{\# exposed controls matched with unexposed cases}}$$

EXAMPLE: Calculate the odds ratio and 99% test-based confidence limits for the quadruplets.

\# unexposed controls matched to exposed cases = (0)(1)+(1)(1)+(2)(5)+(3)(4) = 23
\# exposed controls matched to unexposed cases = (3)(0)+(2)(1)+(1)(1)+(0)(1) = 3

Odds ratio = (23 / 3) = 7.67

Lower 99% limit = $7.67^{[1 - (2.58/3.09)]} = 1.4$
Upper 99% limit = $7.67^{[1 + (2.58/3.09)]} = 42.1$

NOTE: If time permits during class or for review later, calculate the odds ratio and 99% test-based limits for the triplets. The Z-value for a 99% confidence interval is 2.58. The instructors will provide you with the answers.

The investigators combined the information from the pairs, triplets, and quadruplets to yield a summary odds ratio of 7.7, 99% confidence limits of 2.1 and 27.8, chi of 4.08, and $p<0.0001$.

Statistical methods for analyzing case-control studies with a variable matching ratio are best done using computer software.

Question 15: Why might the investigators have used 99% confidence intervals?

We noted that the CDC investigators wished to test the hypothesis that one or more brands of tampons might be more strongly associated with TSS than other brands were. To test that hypothesis, the data were analyzed as shown in Table 9.

Table 9. Brand-specific tampon use among TSS cases and controls who used a single brand exclusively, CDC-2, 1980 (NOTE: Values in cells are percentages, not numbers of users)

	Cases	Non-cases	
Rely	71	26	crude OR = 7.0,
All others	29	74	matched OR = 7.7
Playtex	19	27	crude OR = 0.7
All others	81	74	matched OR = 0.7
Tampax	5	26	crude OR = 0.2,
All others	95	74	matched OR = 0.1
Kotex	2.5	11	crude OR = 0.2,
All others	97.5	89	matched OR = 0.2
OB	2.5	11	crude OR = 0.2,
All others	97.5	89	matched OR = 0.3

Question 16: Can manufacturers of tampons other than Rely claim that their brands protect against TSS?

PART II - CONCLUSION

The results of the CDC-2 study were published in the *MMWR* of September 19, 1980. The study showed a strong and statistically significant association between Rely brand tampons and TSS. On September 22, 1980, after discussions among CDC, the Food and Drug Administration (FDA), and Proctor and Gamble (the manufacturers of Rely), the company voluntarily withdrew Rely tampons from the market.

At about the same time, CDC stopped accepting direct case reports of TSS, and instead referred persons who wished to report a case to their state health departments. In addition, the number of menstruating women using tampons declined from about 70% to about 50%.

Subsequently, the number of TSS cases reported to CDC declined. Although CDC attributed the decline to the withdrawal of Rely and the overall reduction in tampon use, critics have charged that the decrease in reported cases may have been due to the change in the reporting system.

In 1982, the FDA required the labeling of tampons to advise women to use the lowest absorbency tampons compatible with their needs. On January 1, 1983, Toxic Shock Syndrome became a nationally reportable disease. In March 1990, ten years after the original epidemic of TSS, the FDA instituted standardized absorbency labeling of tampons.

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