



Centers for Disease Control and Prevention
Epidemiology Program Office
Case Studies in Applied Epidemiology
No. 831-699

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;
- 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 each year.



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, hypotension, diffuse rash, desquamation, 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 3 studies, limited to menstruating women, are summarized in Tables 1, 2, and 3.

Table 1

CDC-1*

	Cases	Controls
tampon users	50	43
non-users	0	7

reported p = 0.02

Table 2

WISCONSIN

	Cases	Controls
tampon users	30	71
non-users	1	22

reported p = 0.014

Table 3

UTAH

	Cases	Controls
tampon users	12	32
non-users	0	8

p not reported,
but p = 0.20

* 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 2 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	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: Calculate 95% test-based confidence limits using the following formula:

$$\text{Lower 95\% limit} = \text{OR}^{1 - (Z/\text{chi})}$$

$$\text{Upper 95\% limit} = \text{OR}^{1 + (Z/\text{chi})}$$

(chi = square root
of chi-square)

For 95% CL's, $Z = 1.96$

Question 7: Describe your results.

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

Question 9: Which 2-by-2 table format is appropriate for this study?

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

For the moment, 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 women who use other brands.

Question 11: 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?

Since age frequently is a confounding variable, the following (fictitious) marketing research data might help you in determining whether age is indeed 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, Women Age 12-49 Years, United States, 1980

<u>Brand</u>	<u># of Users</u>	<u>% of All Users</u>	<u># TSS Cases</u>	<u>Risk of TSS per 100,000 users</u>
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, By Age, among Women Age 12-49 Years, United States, 1980

Women aged 12-29 years

<u>Brand</u>	<u># of Users</u>	<u>% of All Users</u>	<u># TSS Cases</u>	<u>Risk of TSS per 100,000 users</u>
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

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

Question 12: Calculate relative risks for the data in Tables 6 and 7. Is confounding present? How can you tell? What can you do about it?

Question 13: What are the advantages and disadvantages of matching?

Question 14: As in Question 11, 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 15: 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.

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	OR = 7.7 (1.4, 42.1) chi-square = 9.59 chi = 3.09 2-tailed p = 0.002
	No	0	1	1	1	3	
		1	2	6	5	14 quadruplets	

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	OR = ____ (____, ____) chi-square = 7.54 chi = 2.75 2-tailed p = 0.006
	No	0	3	4	7	
		3	6	11	20 triplets	

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.

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

$$\# \text{ exposed controls matched to unexposed cases} = (3)(0) + (2)(1) + (1)(1) + (0)(1) = 3$$

$$\text{Odds ratio} = (23 / 3) = 7.67$$

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

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

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 16: 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 below.

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

Question 17: 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. While 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.

REFERENCES

1. CDC-1 Study
Shands KN, Schmid GP, Dan BB, et al. Toxic-shock syndrome in menstruating women: association with tampon use and *Staphylococcus aureus* and clinical features in 52 cases. *N Engl J Med* 1980;303:1436-42.
2. CDC-2 Study
Schlech WF, Shands KN, Reingold AL, Dan BB, et al. Risk factors for development of toxic shock syndrome: association with a tampon brand. *JAMA* 1982;248:835-9.
3. Wisconsin study
Davis JP, Chesney PJ, Wand PJ, LaVenture M, et al. Toxic-shock syndrome: epidemiologic features, recurrence, risk factors, and prevention. *N Engl J Med* 1980;303:1429-35.
4. Criticism of CDC studies
Harvey M, Horwitz RI, Feinstein AR. Toxic shock and tampons: evaluation of the epidemiologic evidence. *JAMA* 1982;248:840-6.
5. Brief ten-year perspective
CDC. Reduced incidence of menstrual toxic-shock syndrome - United States, January 1, 1979-March 31, 1990. *MMWR* 1990;39:421-3.
6. Expanded ten-year perspective
Schuchat A, Broome C. Toxic shock syndrome and tampons. *Epidemiol Reviews* 1991;13:99-112.
7. Reprint of May 23, 1980 MMWR article with updated editorial note
CDC. Toxic-shock syndrome. *MMWR* 1997;46:492-5.