Instructor's Guide to APPENDIX 5—CASE STUDY
TAMPONS AND TOXIC SHOCK SYNDROME

**Question 1**  What biases would you be concerned about with these surveillance reports?

**Answer 1**  Publicity bias (as a form of detection / diagnostic bias) is when a diagnosis is more likely to be made or a case is more likely to be reported in persons exposed to a putative cause. In this case the publicity about tampon use made physicians more likely to recognize TSS in menstruating women than in non-menstruating women. Thus, publicity bias represents a type of information bias.

**Question 2**  Using the small sample size odds ratio formula (formula 11.3) calculate the odds ratios for each of the case–control studies in Tables A5.1 - A5.3. From these data, would you conclude that TSS is associated with tampon use? Do you consider the Utah study to be consistent or inconsistent with the other two studies?

**Answer 2**  At this point it might be worth discussing the undefined nature of odds ratio with zeros in the $A_b$ or $B_b$ cell. For example, in the CDC-1 study the OR estimate = $(50)(7)/(43)(0) = undefined$ with a limit of infinity. (i.e., as the denominator gets smaller, the ratio gets infinitely larger.) Addition of the 0.5 to each table cell can be justified in terms of unbiasing the statistical expectation of the odds ratio (Jewell, 1986). In addition, this provides a “quick-and-dirty” method for estimating the odds ratio when there are zero cells in the denominator of the cross-product ratio. However, some epidemiologists consider the small sample size formula a form of fudging and advise against its use.

The small sample size adjusted odds ratio are as follows

- **CDC-1 Study:** $OR_{small \ sample} = (50.5)(7.5)/(0.5)(43.5) = 17.4$
- **Wisconsin Study:** $OR_{small \ sample} = (30.5)(22.5)/(1.5)(71.5) = 6.4$
- **Utah Study:** $OR_{small \ sample} = (12.5)(8.5)/(0.5)(32.5) = 6.5$

These show strong positive associations throughout.

**Question 3a**  Comment on the difference between Table A5.4 and the previous tables.

**Answer 3a**  Table A5.4 shows the 52 matched-paris (representing 104 people). The matched-pair format is much more appropriate for these data. When a study is based on matched pairs, the pairs must be maintained in the analysis. Otherwise, the results will be biased.

**Question 3b**  How many cases used tampons continually?

**Answer 3b**  49

**Question 3c**  How many cases did not use tampons continually?

**Answer 3c**  3

**Question 3d**  How many controls used tampons continually?
Answer 3d  34

Question 3e  How many controls did not use tampons continually?
Answer 3e  18

Optional: The instructor may wish to show what the data would look like in a 2-by-2 table in order to reinforce the idea that matched-pair analysis is distinct from independent analysis. Here is how the 104 cases and controls would distribute themselves if the match was broken:

<table>
<thead>
<tr>
<th>Tampon Use</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>49</td>
<td>34</td>
</tr>
<tr>
<td>−</td>
<td>3</td>
<td>18</td>
</tr>
</tbody>
</table>

|      | 52    | 18      | 104     |

Question 3f  Calculate the odds ratio estimate and a 95% confidence interval for the odds ratio parameter.

Answer 3f  Odds ratio estimate = 16 / 1 = 16. I used EpiCalc2000 to derive a 95% confidence interval of (2.25, 323.87).

Question 3g  Calculate McNemar’s chi-square statistic and p value for these data. Interpret your results.

Answer 3g  McNemar’s chi-square (continuity corrected) = (|16 - 1| - 1)^2 / (16 + 1) = 11.53 with 1 df, p = .00069.

Question 3h  Discuss your results.

The study demonstrates a strong positive association between TSS and continual tampon use. This association is “statistically significant” (a much misunderstood term, see Chapter 13.3), providing strong evidence against the null hypothesis. These statements should be made in full view of the validity assumption we have put on the data. From our rudimentary understanding of these studies, however, it should be clear that the main problem with the study isn’t imprecision, but is bias. The most problematic bias discussed so far is detection bias (see Answer 1). Other biases may be operating as well (e.g., information bias and confounding). Students therefore should be warned to interpret the data cautiously.

Question 3i  Have you been given enough information to decide whether the association is causal?

This question gives you the opportunity to discuss the abstract nature of causal inference. You might raise the issue of multicausality (Chapter 2) and Hill’s causal framework (Chapter 16.3). Hill’s causal framework includes the following criteria: (1) Strength of association (2) Consistency (3) Specificity (4) Temporality (5) Biological gradient (6) Plausibility (7) Coherence (8) Experimentation and (9) Analogy. You might discuss if evidence of each type has been presented in the case study so far.
**Question 4** List specific types of selection and information biases that may have been introduced by the MMWR reports, the intense publicity, and the nature of the disease?

**Answer 4**

Selection biases:

1. Tampon users with symptoms might be more likely to seek medical care.
2. Physicians may be more likely to report TSS if a woman is using tampons.

Information biases:

1. Physicians may be more likely to diagnose TSS in tampon users.
2. Women with TSS may be more likely to recall using tampons (esp. Rely brand) than controls.
3. Because of the potential for lawsuits, women with TSS may falsify their use of Rely brand tampons.

**Question 5** Assuming that you will 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?

**Answer 5** The exposure status of controls should be a random reflection of the source population that gave rise to cases (i.e., the controls should represent the study base). A woman should be included as a control only if she could have been included as a case had she come down with TSS. The selection of controls, therefore, depends on how cases were identified. This, in turn, depends on the hypothesis you are testing. If you wish to determine whether a specific brand of tampons is more strongly associated with TSS, you should restrict potential controls to tampon users. Note that by making such a restriction you would no longer be able to confirm the tampon-TSS association, as there would be no fully nonexposed group.

An alternative approach would be to use a study menstruating women of a certain age range. This would allow estimation of odds ratio associated with any and each brand of tampon. However, the inclusion of all menstruating women as potential controls would make study more susceptible to the information and selection biases discussed in Answer 4, above. This shows how each study options may have pros and cons, depending on how the question is framed.

Another option: You might want to preclude the analysis of mixed-brand users, as mixing brands may amplify risk or perhaps be protective.

Sources of controls include (a) women hospitalized for other conditions, (b) neighborhood controls, (c) friend controls, and (d) a random selection of women from the community. Again, the “best” source of controls is debatable and depends (somewhat) on the question being asked. (See §11.5 for comments on the selection of controls in case–control studies).

**Question 6a** Calculate risk ratio for the data in Tables A5.5

**Answer 6a** $RR = \frac{9.2 \times 10^{-5}}{1.3 \times 10^{-5}} = 7.1$
Question 6b  Calculate risk ratio separately for the younger and older age groups in Table A5.6.

\[ RR_{12-29\text{-year-olds}} = \frac{9.4 \times 10^{-5}}{1.9 \times 10^{-5}} = 4.9 \]
\[ RR_{30-49\text{-year-olds}} = \frac{3.3 \times 10^{-5}}{0.67 \times 10^{-5}} = 4.9 \]

Question 6c  Is there evidence of confounding?

Evidence of confounding is present since strata-specific odds ratios differ from the crude odds ratio.

Question 6d  What can you do to control for confounding?

You can stratify the data and calculate a M-H summary odds ratio for the data (see Chapter 14).

Question 6e  What are the properties of a confounder? Does age fulfill these properties in considering the brand-X-TSS association?

Answer 6e  The properties of a confounder are

(1) They are associated with the exposure in the source population.
(2) They are independent risk factors for the disease.

Since age is associated with brand loyalty while also being relate to TSS, age fulfills the properties of a confounder. (In addition, age is not intermediate in the causal pathway between the tampon brand preference and TSS, and is not a consequence of the disease.)

Question 7  What are the advantages and disadvantages of matching?

Advantages:

(1) Can be used to control for confounding (when applied properly).
(2) Can be a practical and convenient way to sample.

Disadvantages:

(1) Can no longer evaluate the effects of factors which have been matched on.
(2) If applied too rigidly may make it difficult to find controls.
(3) Overmatching results in loss of statistical precision.

Question 8  In your study, would you match? Why or why not? On which characteristics would you match? What type of matching would you use?

Answer 8  Available information suggested that age and geographic region may be related to risk and reporting rates. It is also plausible that age and geography were related to tampon use. Therefore, these factors could be used as matching criteria.

Since cases come from various parts of the country, it seems practical to match on locale. Age must also be addressed, and matching is one way to do this. (Alternatively, we might use stratified analysis or a
regression models to control for age and locale.)

At the time of the study, pair-matching was a more popular technique to control for confounding than it is today. We now better know the limitations and disadvantages of pair-matching. In brief, two basic types of matching exist: pair-matching and frequency-matching. In pair-matching, a case is identified and one or more controls is chosen per case, with controls matched on various factors. Frequency-matching selects from pools of people with similar characteristics, as determined before the time of the study from preliminary surveys or a log of people in the population. We currently believe that frequency-matching is more efficient that pair-matching, when it is available. However, the only practical way to achieve any type of match at the time of the study was with pair-matching.

Question 9  Do you agree with the CDC-2 investigators’ decision to use friends or acquaintances as controls?

Answer 9  Pair-matching was a reasonable alternative given the circumstances because it was a practical and quick way to get controls. Moreover, once identified, friend controls were likely to cooperate with the investigators.

An objection to using friend controls is because of overmatching. Overmatching occurs when controls are matched too closely to cases, diminishing the ability to detect any association. The result is to have an excess of concordant case–control pairs. Concordant case–control pairs are ignored during case–control analyses—they “fall out”—since they contribute no information about the exposure-disease relation being studied. This causes a loss of statistical power and precision.

Use of friend controls in the current study may have overmatched n brand of tampon use. Friends tend to shop together or in the same stores. Stores may have a limited number of brands of tampons that they stock. Also, tampon brand choice may be influenced by a friends opinion. This may result in an overmatching which, as stated, would diminish the ability to detect the association between tampon brand and TSS.

In addition, a common misunderstanding is that the match itself control for the confounding variable. This is not true for case–control studies. The match will control for the confounding variable only after the proper analysis is instituted. As a matter of fact, analyzing matched-pair data as if case selection was independent of control selection will introduce a bias into the analysis which may bias the odds ratio either toward or away from the null. (The more common bias is toward the null.)

Question 10  Calculate the odds ratio for the triplets. Interpret this finding.

Answer 10  For the triplets (2:1 matches)

No. of unexposed controls matched with exposed cases = (3)(0) + (3)(1) + (7)(2) = 17
No. of exposed controls matched with unexposed cases = (0)(2) + (3)(1) + (4)(0) = 3

\[ \hat{\psi} = \frac{17}{3} = 5.67 \] . Both the 3:1 tuples and 2:1 tuples demonstrate a strong positive association in between Rely brand tampon and TSS.
**Question 11** Only the Rely brand tampons shows an increase in risk. All other tampon brands have odds ratios less than 1. Can manufacturers of tampons other than Rely claim that their brands protect against TSS?

**Answer 11** No. Odds ratios of less than 1 in the other brands reflects the fact that they are being compared to all other brands, including the Rely tampon users. In order to make a claim of a protective effects, there would have had to have been a “clean” non-exposed group. For example, you would have had to compare Playtex brand to napkin (non-tampon) users. Even here, it would be a stretch to claim a protective effective based on any statistical finding. “Protection” implies a biological effect. Biological effects cannot be ascertained directly from statistical results alone.