The Evidence for Efficacy of HPV Vaccines: Investigations in Categorical Data Analysis

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Abstract

Recent approval of HPV vaccines and their widespread provision to young women provide an interesting context to gain experience with the application of statistical methods in current research. We demonstrate how we have used data extracted from a meta-analysis examining the efficacy of HPV vaccines in clinical trials with students in applied statistics courses at both introductory and intermediate university levels. The data are suitable for various techniques in categorical data analysis including comparison of proportions, analysis of contingency tables, logistic regression and log-linear models. These data are relevant to all young people and, because of their health science context, can be used in courses in biostatistics or the health sciences as they allow for further discussion of meta-analyses and randomized controlled trials. We also discuss how we have used these data to promote discussion of statistical issues such as statistical versus practical significance, independence, and a common misconception involving the interpretation of *p*-values.

1. Introduction

For many years, data from the Salk Polio Vaccine trials (see, e.g., Freedman et al. 2007) and the Physicians' Health Study (see Physicians' Health Study 2009) have been used in our introductory statistics courses as examples of randomized controlled experiments, inference for two proportions, and the chi-square test of homogeneity. While these studies are compelling examples of medical research, current students see them as dated. Motivated by the desire to have a modern example that resonates with current students, we decided to search for data to support the efficacy of the new vaccines for human papillomavirus (HPV). A recent meta-analysis (Lu et al. 2011) provides summaries of the results of seven randomized controlled trials investigating three HPV vaccines.

In addition to providing a very recent example for testing equality of proportions or the analysis of a 2×2 contingency table, the data in Lu et al. (2011) are useful for examples of larger contingency tables, logistic regression, and log-linear models. Additionally, the data provide opportunities for students to think carefully about important considerations in the analysis of categorical data including statistical versus practical significance, sufficient sample size, the need for independent observations, and a common error in analyzing an interaction variable in the context of linear models.

2. The Dataset and Story

2.1 Background

Genital human papillomavirus (HPV) is a common sexually transmitted infection (STI) that causes genital warts and various types of cancer, most notably cervical cancer. According to the Centers for Disease Control and Prevention (2012a), nearly every case of cervical cancer is caused by HPV. The incidence of cervical cancer for any country or region of the world is available at WHO/ICO Information Centre on HPV and Cervical Cancer (2010a). In the USA, it is estimated that more than 11,000 women are diagnosed with cervical cancer each year and almost 4,000 die from the disease (WHO/ICO Information Centre on HPV and Cervical Cancer 2010b). Worldwide, the estimated annual number of new cases of cervical cancer is over 500,000.

There are more than 40 types of HPV (Centers for Disease Control and Prevention 2012a). Types 16 and 18 are the most common types associated with cervical cancer, accounting for more than 70% of cases; after these types 31 and 45 are the most commonly associated with cancer (Brown et al. 2009). Types 6 and 11 are the most common types causing genital warts. Each of the seven studies examined in the meta-analysis by Lu et al. (2011) used one of three vaccines; each vaccine contained virus-like particles of either HPV type 16

only, HPV types 16 and 18, or HPV types 6, 11, 16, and 18.

People infected with HPV often do not have any symptoms and thus are unaware that they are at risk of transmitting the virus to others. It is estimated that 20 million people in the U.S. are infected and 90% of these people are unaware of their infection (Centers for Disease Control and Prevention 2012a). In response to the spread of HPV, pharmaceutical companies developed prophylactic (preventive) vaccines aimed at preventing infection and, in those already infected, activating the immune system to prevent and treat tumors. The development of these new cancer preventive vaccines for HPV is pharmacologically important, as the only other vaccines of this type were developed in 1981 for the prevention of Hepatitis B virus infection due to its association with cancer of the liver (National Cancer Institute 2011).

As we examine in Section 3, the vaccines have been shown to be highly effective and health organizations are recommending widespread vaccination. At the end of 2011, 40 countries had introduced HPV vaccines into their immunization schedules for girls, with three countries also recommending its use for both boys and girls (World Health Organization 2012). For example, the Centers for Disease Control and Prevention, in partnership with the American Academy of Pediatrics, recommend HPV vaccination at age 11 or 12 years for both girls and boys (Centers for Disease Control and Prevention 2012b). In many jurisdictions, the vaccine is administered to girls in school. For example, in Toronto the vaccine is delivered free-of-charge to all girls in grade 8 (City of Toronto 2012).

However because HPV is sexually transmitted, widespread provision of the vaccine is not without controversy. Cervical cancer is rare and regular screening with a Pap test can prevent cervical cancer from occurring in most cases by identifying abnormal cells so that they can be removed before cancer develops (Centers for Disease Control and Prevention 2012a). Moreover, some organizations are concerned that provision of the vaccine condones early sexual activity (see, e.g., Gerson 2012). But a recent study (Bednarczyk et al. 2012) found that incidence rates of markers of sexual activity were not statistically significantly elevated in vaccinated girls compared to unvaccinated girls. Moreover, Kahn et al. (2012) showed that the vaccination provides "herd protection," protecting girls who have not been vaccinated in a community where other girls have been vaccinated. The World Health Organization (2012) recognizes the potential benefit of using HPV vaccination as an entry point into the health system for adolescents in order to promote other health and reproductive services.

This article can be considered as a companion to the Datasets and Stories article by Barat et al. (2011). Barat et al. (2011) examined the characteristics of patients that affect completion of the vaccine's sequence of three shots.

Table 1. Some characteristics of the four studies discussed in this article, extracted from Table 1 of Lu et al. (2011).

Study:	Harper et al.	Koutsky et al.	PATRICIA	FUTURE I
Year of study enrollment	11/2003–07/2004	10/1998–11/1999	05/2004–06/2005	06/2002–05/2003
Sponsor	GlaxoSmithKline	Merck	GlaxoSmithKline	Merck
Vaccine	HPV 16, 18	HPV 16	HPV 16, 18	HPV 6, 11, 16, 18
Control	Placebo	Placebo	Hepatitis A vaccine	Placebo
Age of subjects (years)	15–25	16–25	15–25	16–24
Countries included	3 (from North & South America)	1 (United States)	14 (from Asia-Pacific region, Europe, Australia, and North, South & Central America)	16 (from Asia-Pacific region, Europe, and North, South & Central America)

2.2 The Data

The data we consider here were extracted from the paper by Lu et al. (2011). Lu et al. (2011) conducted a review and meta-analysis of seven randomized controlled trials of HPV vaccines, summarizing HPV type-specific efficacy against precursors of cervical cancer and assessing vaccine safety. In this article, we consider data from four of these studies. See Table 1 for further details. The data can be found in the http://www.amstat.org/publications/jse/v21n3/gibbs/hpv_clinical_trial_data.txt file, and the data documentation can be found in the http://www.amstat.org/publications/jse/v21n3/gibbs/hpv_clinical_trial_data_documentation.txt file. The study subjects were randomly assigned to receive the vaccine or a placebo (or, in one study, a Hepatitis vaccine in place of a placebo) and were followed for approximately three years post-vaccination. Lu et al. (2011) included analyses based on intent-to-treat populations (all subjects enrolled) and per-protocol populations (subjects who completed the sequence of three vaccinations). They also included data for three possible outcomes: persistent HPV infection, cervical lesions of any type (abnormal or precancerous tissue), and high-grade cervical lesions or worse (severely abnormal tissue or cancer). In choosing which of these data to present here, we made the following decisions:

- We chose to limit our analysis to per-protocol populations. The analysis of these populations allow for more tractable discussion of whether the vaccines were indeed

effective in patients who completed the treatment regimen.

- The World Health Organization recommends high-grade cervical lesions or worse as the recommended endpoint for evaluating efficacy of HPV vaccines. This outcome is the primary endpoint in Lu et al. (2011). However, Lu et al. (2011) recognized persistent HPV infection of at least 6 months as an important secondary outcome for the efficacy of the vaccines, noting HPV infection is a necessary precursor of cervical lesions. An infection is considered "persistent" if the same HPV DNA is detected in two consecutive examinations in a period of at least 4 months (Lu et al. 2011). We chose to analyze persistent infections as the accompanying data afford a more interesting case study while still examining an important and relevant health outcome. In particular, this choice also allows for the consideration of HPV types other than those present in the vaccines as persistent HPV infection is the only outcome available for certain types of HPV.

- HPV type 16 is associated with 55% of cervical cancer cases (Lu et al. 2011) and HPV 16 virus-like particles are in all of the vaccines considered in the meta-analysis. The efficacy of the vaccines against persistent HPV 16 infection is discussed in Section 3.2.

- HPV 31 and 45 are the types most commonly associated with cervical cancer that are not specifically covered by any vaccine. Whether or not the vaccines reduce the incidence of infection with these other types is discussed in Section 3.3.

2.3   The Research Questions

In this article, our focus is the evidence for the efficacy of the vaccines. Our analysis centers around two main research questions:

1. Do the vaccines work when they are supposed to? That is, do the vaccines reduce the incidence of persistent infection of HPV 16, for which virus-like particles are present in all HPV vaccines?

2. Do the vaccines also reduce the incidence of persistent infection of other HPV types, specifically HPV 31 and 45, for which there are no type-specific virus-like particles in the vaccines?

As a secondary question, we examine whether there are differences in the incidence of HPV infection among the studies. Any differences that may exist could be attributed to the different vaccines, different patient groups, or different protocols of the various studies.

3. The Analysis and Conclusions

In this section we first give an outline of design considerations which we have used for class discussion. We then describe analysis of the data to answer the research questions pointing out several helpful hints and potential pitfalls along the way. We have used both SAS and R for the analysis of these data. In Tables 6 and 7, we give some output from SAS but it is easily adaptable to any statistical software package.

3.1 Design Considerations

Helpful Hint: All seven of the studies included in the meta-analysis, including the four whose data we consider, are randomized double-blind controlled trials. As always when introducing new sources of data to our classes, we begin with a discussion of the design of the studies. Some of the points of discussion we may raise include:

- How do you know these studies are experiments? (Possible answer: Treatments (HPV vaccine or control) were imposed by the researcher on the participating subjects.)

- Why is it appropriate to carry out an experiment for this research? (Possible answer: We would like to conclude that the vaccine causes reduced infection rates.)

- What is the purpose of the control group? (Possible answer: We expect that some subjects will acquire HPV infections during the study period so we need a comparison group to assess the efficacy of the HPV vaccine at reducing infection rates.)

- In all but one of the studies considered in the meta-analysis, the control group received an inactive placebo. In one of the studies (the PATRICIA study), the control group received a vaccine against Hepatitis A. Why do you think this was done? (Possible answer: Because we found no mention of the reason for this in published papers, we are left to speculate about possible reasons. Perhaps, for ethical reasons or to improve recruitment, the PATRICIA researchers wanted to expose all subjects to the potential benefit of receiving a vaccine with an active ingredient, even if the subjects were randomly assigned to not receive the HPV vaccine.)

- What considerations would go into determining the number of subjects enrolled in each study? (Possible answers: Desired power and Type I error rate, expected rates of infection in the vaccine and control groups.)

Table 2. Counts of the number of subjects who acquired or did not acquire persistent HPV 16 infections, by whether or not the subject received the HPV vaccine, for the Harper, Koutsky, and PATRICIA studies. Extracted from Figure 4 of Lu et al. (2011).

Study:	Harper		Koutsky		PATRICIA	
	HPV 16 infection?		HPV 16 infection?		HPV 16 infection?	
Group	No	Yes	No	Yes	No	Yes
Control	366	19	639	111	5673	345
Vaccine	413	1	748	7	6140	23

- What are the ethical considerations that go into the planning of these studies? (Possible answers: Sample size should be chosen to ensure adequate power so that a practically meaningful difference in infection rates is statistically significant, but should not be too large for unnecessary expense or to expose more subjects than needed to an untested vaccine. There should be sufficient doubt about the efficacy of the vaccine so that it is not unfair that some participants are enrolled in the control group.)

3.2 Research Question 1: Do the vaccines work when they are supposed to?

3.2.1 Analysis of HPV 16 Infections by Study

While various vaccines are designed to protect against one, two, or four HPV types, all of the vaccines include virus-like particles from HPV 16. Are the vaccines successful at reducing the incidence of persistent HPV 16 infection? Lu et al. (2011) give data for the Harper, Koutsky, and PATRICIA studies, which examine persistent infection with HPV 16 as one of the outcomes. Both the Harper and PATRICIA studies used the GlaxoSmith-Kline vaccine that contained virus-like particles for both HPV 16 and 18; the Koutsky study used the Merck vaccine containing virus-like particles for HPV 16 only. All vaccines were administered through injections. The control group in the PATRICIA study received a vaccine against Hepatitis A; the control groups in the Harper and Koutsky studies received injections with no active ingredients. For each study, the observed numbers of subjects in the vaccine and control groups, by whether or not they acquired an HPV 16 infection, are in Table 2. An illustration of these data is given in the mosaic plot in Figure 1.

From Table 2 and Figure 1, it is clear that:

1. The counts of patients who received a vaccine and subsequently acquired a persistent HPV 16 infection are smaller than the counts for patients who received the placebo.
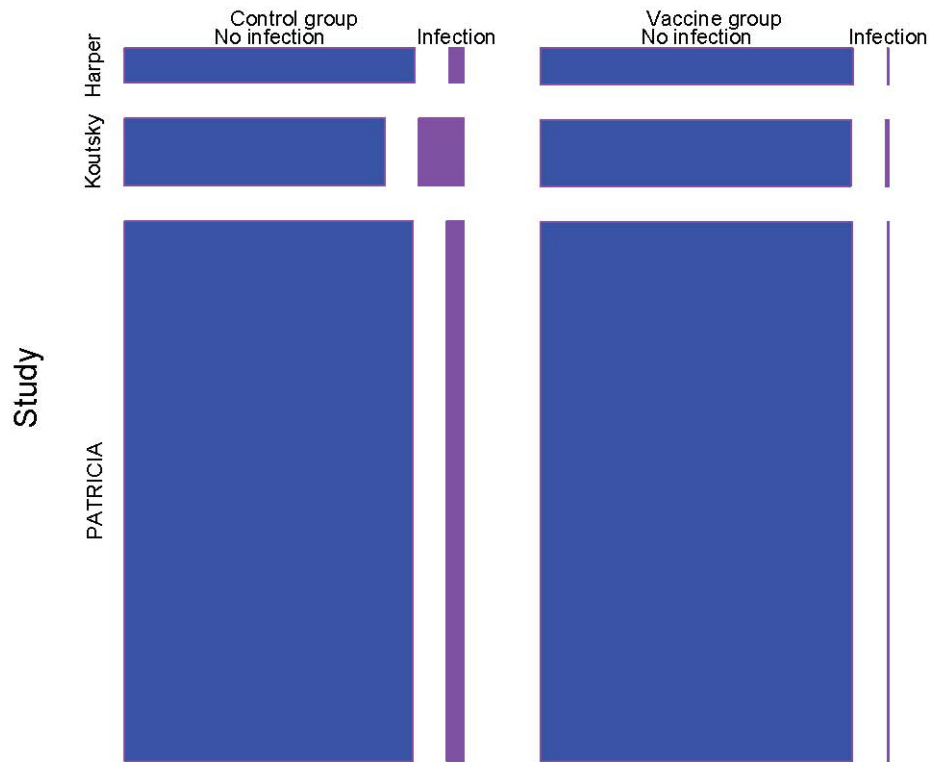
Figure 1.   A mosaic plot illustrating the data in Table 2.

2. The vaccine is not perfect. The outcome of persistent HPV 16 infection occurred in both the vaccinated and control groups.

A natural follow-up question is if these apparent differences in HPV 16 infection rates are statistically significantly different between the vaccine and control groups. In introductory courses for nonmajors, we investigate this question separately for each study through inferential procedures for proportions from two independent samples. Once students have learned analysis procedures for contingency tables, such as the chi-square test of homogeneity or Fisher's Exact Test, we again use these data and compare the results. In our mathematical statistics course which develops the theory of inference based on likelihood ratio tests, we use the 2×2 table for each study to illustrate the likelihood ratio test based on the multinomial distribution. The results for these analyses are given in Table 3. For all studies, there is strong evidence of differences in the proportion of subjects acquiring HPV 16 infection between the vaccine and control groups, with higher rates of acquisition in the control groups.

> *Helpful Hint:* We typically ask students to give a *complete* answer to the question: *"What do you learn from the given output from statistical software?"* For

Table 3.   Results of the analysis of the data in Table 2. Continuity corrections were not used.

Study:	Harper	Koutsky	PATRICIA
Infection rate for control group	4.9%	14.8%	5.7%
Infection rate for vaccine interval	0.2%	0.9%	0.4%
95% CI for $p_{\text{control}} - p_{\text{vaccine}}$	$(0.025, 0.069)$	$(0.112, 0.165)$	$(0.048, 0.060)$
Test for equality of proportions			
Test statistic	4.2	10.0	17.3
p-value	< 0.0001	< 0.0001	< 0.0001
Chi-square test of homogeneity			
Test statistic	18.0	100.2	298.5
p-value	< 0.0001	< 0.0001	< 0.0001
Multinomial LRT			
Test statistic	21.6	119.0	354.8
p-value	< 0.0001	< 0.0001	< 0.0001

example, Figure 2 shows the table produced by SAS from the FREQ procedure as part of the analysis of the HPV 16 infection data from the Koutsky study. By default, SAS produces overall, row, and column percentages. Many students, especially those in our introductory calculus-based courses, only quote an appropriate p-value and state that there is strong evidence that the proportion of subjects with HPV 16 infections differs between the control and vaccine groups. Such a simple answer without an explanation of how they differ is not an indication of complete understanding. We have found it helpful to prompt students with questions such as: *"Which group has a higher infection rate?" "By how much?" "Is this a meaningful difference?"* We believe that it is important to persistently emphasize the need to express the results in a way that is relevant and meaningful to those who will be using the results. Moreover, when presented with all possible percentages as in Figure 2, we have found that students need guidance and experience before they are confident with making the decision of which percentages to quote to tell the story most clearly.

Helpful Hint: Infection rates in the vaccine groups are very small. In the control groups, they are much larger. As noted above these differences are statistically significant. Given the cost of administration and possible risk of adverse events associated with any vaccine, we ask the students to consider whether the differences in the incidence rates are compelling enough to make a case for widespread provision. This question helps to emphasize that statistical significance is only part of any data analysis and that practical significance must also be considered.

The FREQ Procedure

Frequency Percent Row Pct Col Pct	Table of group by event		
		event	
group	No	Yes	Total
Control	639	111	750
	42.46	7.38	49.83
	85.20	14.80	
	46.07	94.07	
Vaccine	748	7	755
	49.70	0.47	50.17
	99.07	0.93	
	53.93	5.93	
Total	1387	118	1505
	92.16	7.84	100.00

Figure 2. SAS output from the FREQ procedure for the analysis of persistent HPV 16 infection for the Koutsky study.

Potential Pitfall: As a result of the small sample size combined with the small incidence rate in the vaccine group, the usual rule-of-thumb requiring expected counts of 5 in each cell does not hold in the Harper study. This lack of observations may cause the asymptotic tests to be inaccurate. Students should be on the look-out for potential difficulties in applying the methods, and be prepared with alternatives including, for example, randomization tests.

Helpful Hint: For more advanced students who have studied all of the methods of analysis in Table 3, we compare and contrast the results from the three methods. Although, in this case, they all result in the same conclusion, the test statistics and corresponding *p*-values differ. This allows us to engage our students in sophisticated statistical reasoning, evaluating different methods that could be used with the same research question and data, reviewing the assumptions of each, and their strengths and limitations, and deciding which, if any, is most appropriate.

In our advanced course which covers generalized linear models, we review the above methods of analysis before introducing binomial logistic regression and log-linear models which can also be used to analyze these data.

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3.2.2 Are there variations in infection rates among studies?

From the results in Table 3, we note that it appears that more people acquire HPV infections in the Koutsky study group. As noted in Table 1, the studies have different populations, with different countries included in each study, and differences in the prevalence of HPV infection among these populations will likely result in corresponding differences in the probabilities of becoming infected. To investigate this, we can examine whether the HPV infection rates are consistent across studies. Students in introductory statistics classes, whose most sophisticated tool for categorical data analysis is the chi-square test of homogeneity for $r \times c$ contingency tables, are limited in their ability to investigate this. One possible solution is to consider vaccine and control groups one at a time, and examine for each of these the 3×2 table of study by HPV infection status.

For the control group, there is strong evidence that the proportion of subjects acquiring an HPV 16 infection differs with study (chi-square test of homogeneity with 2 degrees of freedom, test statistic = 90.3, p-value$< .0001$). From Table 3, we see that the control group HPV 16 infection rate is almost 10% higher in the Koutsky study than in the other two studies. Looking at the study characteristics in Table 1, we see that the Koutsky study took place more than five years prior to the Harper and PATRICIA studies, and had a less diverse set of subjects (recruiting only from the United States). There is no evidence that the different control group vaccine used in the PATRICIA study (Hepatitis A vaccine, rather than a placebo) is associated with differences in the control group HPV infection rates among studies. In contrast, there is only very weak evidence of differences among studies in the vaccine group (chi-square test of homogeneity with 2 degrees of freedom, test statistic $= 5.2$, p-value$= 0.07$). Although different studies used different vaccines, we do not have strong evidence of differences in HPV 16 infection rates in vaccinated subjects.

> *Potential Pitfall:* Because the p-value is small for the test of differences among studies using the control group data, and the corresponding p-value is relatively large for the vaccine group data, it is extremely tempting to conclude that the differences in the proportions infected in the control and vaccine groups vary significantly among studies. This is an extremely common error (see Matthews and Altman 1996). It follows from the incorrect statement that a large p-value means that there is no difference, instead of the correct statement that a large p-value means that no evidence of a difference has been found. Differences in p-values among groups can occur when there are differences among the groups, but also when there are differences in the standard errors of the estimates of the quantity being compared. The data in Table 2 provide an excellent opportunity to discuss this misconception, why it occurs,
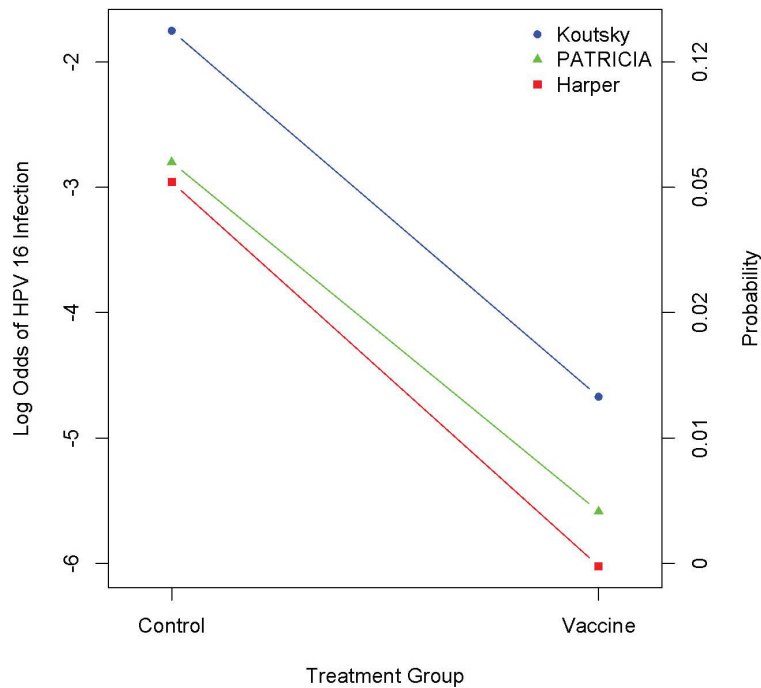
Figure 3.   Log odds of acquiring an HPV 16 infection for the control and vaccine groups for each of the three studies in Table 2.

> and to motivate the need for a more sophisticated model (which would allow the significance of study-treatment group interaction to be examined).

Figure 3 shows the log odds of acquiring an HPV infection by treatment group for each of the Harper, Koutsky, and PATRICIA studies. We can see that the log odds are higher for the control group than the vaccine group, by a similar amount for each study. And the log odds of infection are higher in the Koutsky study group than in the other two studies.

In order to examine whether the possible differences among studies in incidence of HPV 16 infection are statistically significant, a model that includes their interaction is necessary. There are two possible analyses: a binomial logistic regression model and log-linear models. Partial SAS output for the fitted logistic regression and log-linear models is given in Table 6 and Table 7. In this analysis, `group` is a categorical variable indicating treatment assignment with values vaccine and control. In the logistic regression, we are modelling the odds of HPV infection. In the log-linear models, the variable `event` takes on the values Yes and No, indicating whether or not a subject has an HPV 16 infection.

Since whether or not a subject acquires a persistent HPV 16 infection can be considered a response variable, a binomial logistic regression analysis can be used to evaluate the effects of the vaccine versus the control group and how these differ across studies on the odds of

acquiring an HPV 16 infection. In the logistic regression analysis for these data:

- In the saturated model, the Wald test for the interaction between group and study has a large p-value ($p = 0.93$), indicating that the differences in infection rates among studies are not statistically significantly different between the control and vaccine groups, illustrating the potential pitfall that can result from the individual analysis of the two 3×2 contingency tables.

- The reduced model indicates strong evidence of differences in infection rates among studies ($p < 0.0001$) and between the vaccine and control groups ($p < 0.0001$).

Potential Pitfall: Since there are three studies, the group-study interaction involves two terms in the linear model and the test statistic for the likelihood ratio test comparing the saturated and reduced model has two degrees of freedom. We have found that, because one effect (the interaction) is being tested, students expect the test statistic to be an observation from a distribution with one degree of freedom. We find it helpful to have students write out the saturated and reduced models using indicator variables so that they can see that the significance test for the interaction term corresponds to two terms in the saturated model.

The corresponding log-linear model has statistically significant interactions for event and group ($p < 0.0001$) and for event and study ($p < 0.0001$) but no other significant interactions. Whether or not a subject acquires an HPV 16 infection is associated with both the study enrolled in and whether the subject is in the vaccine or control group. This partial independence interpretation is consistent with the conclusions from the logistic regression analysis.

Helpful Hint: In our more advanced statistical methods course, we often have students carry out both the logistic regression and log-linear model analysis to convince themselves of the equivalence of these approaches. Many students have difficulty interpreting the more complicated dependency structures in log-linear models, and we find the comparison to the equivalent, but apparently simpler, logistic regression model to be helpful.

3.3 Research Question 2: Do the vaccines offer protection against other HPV types?

HPV vaccines seem to reduce infection incidence rates for HPV types that are not even in the vaccine. We now examine vaccine efficacy for the two HPV types most commonly

Table 4. Counts of the number of subjects who acquired or did not acquire persistent HPV 31 and 45 infections, by whether or not the subject received the HPV vaccine, for the FUTURE I and PATRICIA studies. Extracted from Figure 6 of Lu et al. (2011).

Study:	FUTURE I				PATRICIA			
	HPV 31 infection?		HPV 45 infection?		HPV 31 infection?		HPV 45 infection?	
Group	No	Yes	No	Yes	No	Yes	No	Yes
Control	975	57	1006	26	7183	215	7446	94
Vaccine	1005	31	1012	24	7348	46	7564	23

related to cervical cancer which are not in any vaccines, HPV 31 and HPV 45 (Brown et al. 2009). For the studies examined in Lu et al. (2011), data on HPV type 31 and 45 infections are available for two studies, FUTURE I and PATRICIA. The vaccine in the PATRICIA study contains virus-like particles for HPV types 16 and 18; the vaccine used in the FUTURE I study contains virus-like particles for HPV types 6, 11, 16, and 18.

Table 4 and Table 5 give the data and results for each study. Figure 4 illustrates these data in mosaic plots and Figure 5 shows the log odds of infection for the investigation of whether the vaccines reduce the incidence of persistent infection with HPV types 31 and 45. In Figure 5, we see that the log-odds of infection with HPV 31 are higher in the control group than the vaccine group, but that the difference between the treatment groups is greater in the PATRICIA study than in the FUTURE I study, perhaps a reflection of the different vaccines used in the two studies (see Table 1). From Table 5, we see that there is strong evidence of a difference in the proportion of subjects infected with HPV 31 between the vaccine and control groups in both studies.

For HPV 45, the difference between treatment groups in the log odds of infection is large in the PATRICIA study but very small in the FUTURE I study, and from Table 5 we see that there is strong evidence of a difference in the PATRICIA study, but no evidence of a difference in the FUTURE I study. This might possibly be due to the different vaccines used in the two studies (see Table 1). As noted in a similar situation discussed in the potential pitfall in Section 3.2, however, we cannot conclude that there is a statistically significant difference between the studies in the effectiveness of the vaccines in preventing HPV 45 infection.

Helpful Hint: The sample size in the PATRICIA study is approximately seven times that of the FUTURE I study, as is emphasized in Figure 4. We have found it helpful to have the students consider how this is reflected in the results in Table 5.

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Table 5. Results of the analysis of the data in Table 4. Continuity corrections were not used.

Study:	FUTURE I		PATRICIA	
	HPV 31	HPV 45	HPV 31	HPV 45
Infection rate for control group	5.5%	2.5%	2.9%	1.2%
Infection rate for vaccine interval	3.0%	2.3%	0.6%	0.3%
95% CI for $p_{\text{control}} - p_{\text{vaccine}}$	$(0.008, 0.043)$	$(-0.011, 0.015)$	$(0.019, 0.027)$	$(0.007, 0.012)$
Test for equality of proportions				
Test statistic	2.9	0.30	10.5	6.6
p-value	0.004	0.76	< 0.0001	< 0.0001
Chi-square test of homogeneity				
Test statistic	8.1	0.09	111.3	43.9
p-value	0.004	0.76	< 0.0001	< 0.0001
Multinomial LRT				
Test statistic	8.2	0.76	120.6	47.0
p-value	0.004	0.76	< 0.0001	< 0.0001

Potential Pitfall: At this point, it is extremely tempting to combine the data in Table 4 to create a dataset for each study with three outcomes: HPV 31 infection, HPV 45 infection, and infection with neither. However, we do not have enough information to do so; it is quite possible that some subjects have acquired infection with more than one HPV type. The possibility of creating a contingency table in which some subjects have been counted more than once and the implications for methods of analysis requiring independent observations is an important consideration for students to grapple with.

Alternative Application: For each HPV type, it is possible to combine the data from the two studies using logistic regression or log-linear models. For both HPV 31 and 45 the group-study interaction is significant so saturated models are necessary.

3.4 Other Methods and Outcomes

The data considered here are appropriate as illustrations of a variety of additional topics, particularly in biostatistics. In particular, these data would serve as an excellent example for:

- Relative risk or vaccine efficacy. (Efficacy is the main outcome in all of the studies whose results are quoted here; relative risk is used in the meta-analysis.)

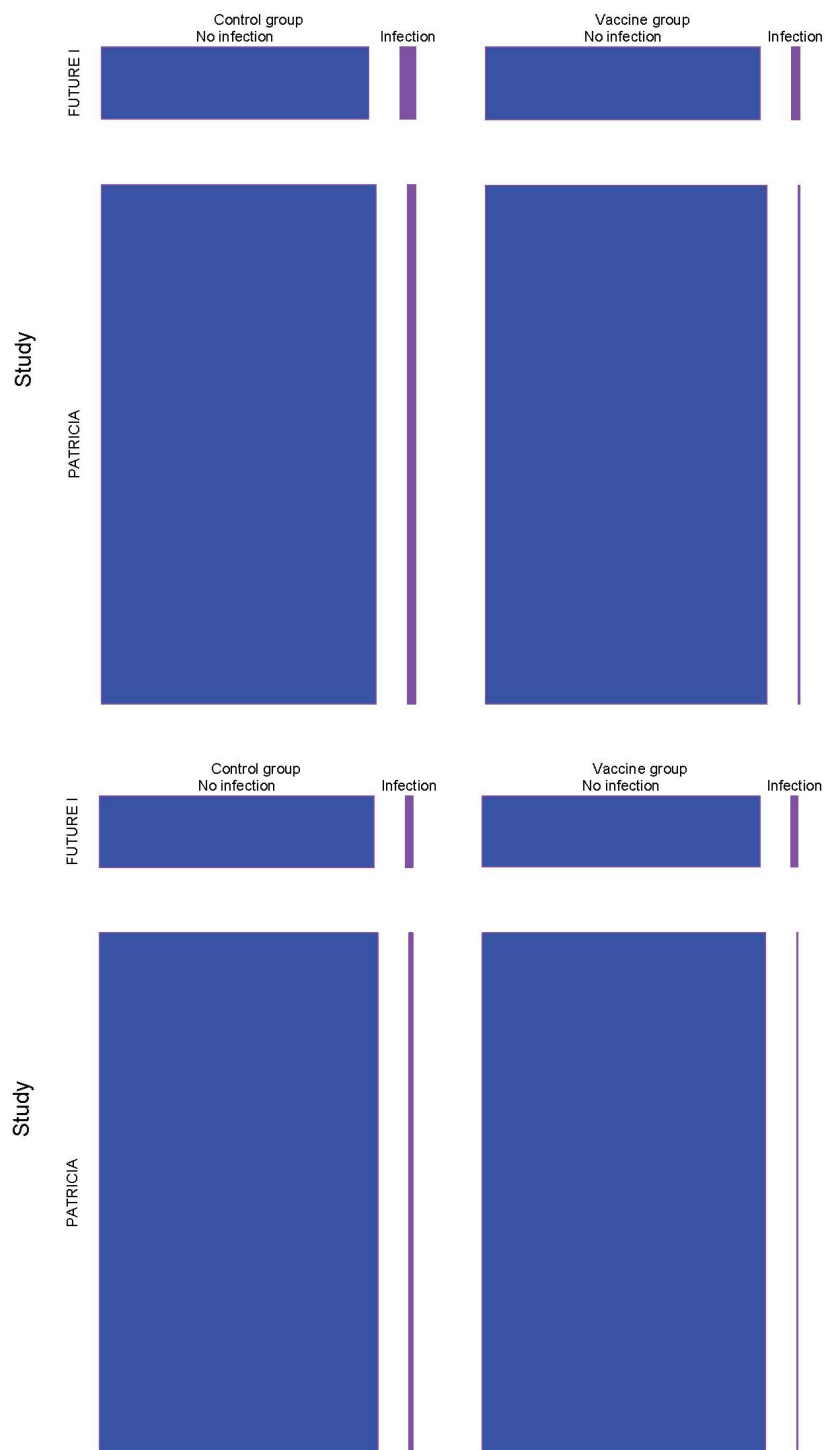- Odds ratio.

- The design of clinical trials.

Figure 4. Mosaic plots for the data in Table 4. The upper plot illustrates the HPV 31 infection rate data and the lower plot illustrates the HPV 45 infection rate data.
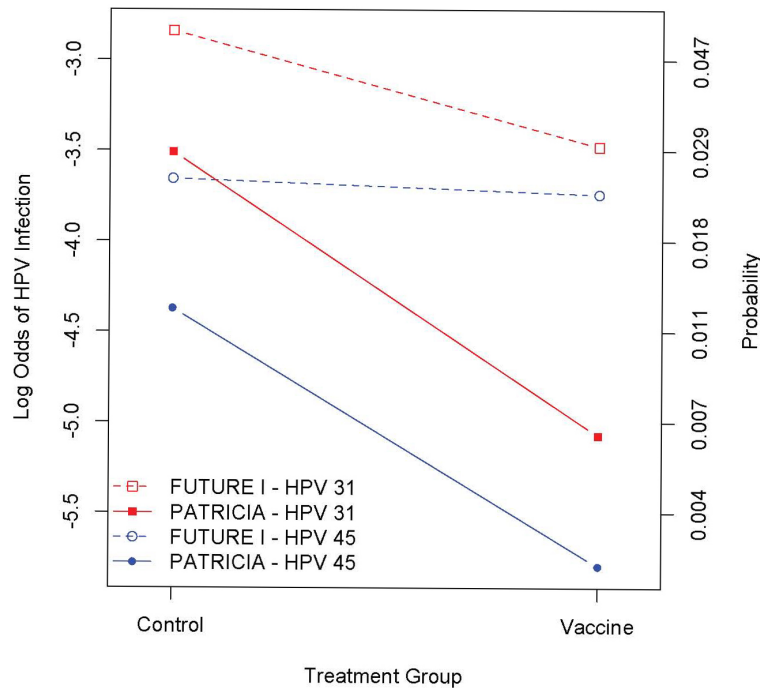
Figure 5.   Log odds of acquiring an infection with HPV 31 and HPV 45 for the control and vaccine groups for the two studies in Table 4.

- Intent-to-treat versus per-protocol populations.

- Meta-analysis.

Alternative Application: The figures in Lu et al. (2011) offer many other options for additional data for which similar analyses to those we have discussed can be employed. Students or their instructors can mine the paper for data with cervical lesions as the outcome, data for intent-to-treat populations, results from two other studies, incidence of adverse events, and results for HPV types 18, 33, 52, and 58.

4. Conclusion

The investigation of the data reported here brings to life some important and current scientific research that is applicable to teenagers and young adults. Furthermore, the data allow for applications of statistical methods that are typically covered in both introductory and advanced courses, while giving students some important experience with potential pitfalls.

Table 6.   Edited SAS output for the logistic regression with outcome HPV 16 infection, saturated and reduced models.

Saturated Model

The LOGISTIC Procedure

Class Level Information

Class	Value	Design Variables	
group	Control	1	
	Vaccine	0	
study	Harper	1	0
	Koutsky	0	1
	Patricia	0	0

Deviance and Pearson Goodness-of-Fit Statistics

Criterion	Value	DF	Value/DF	Pr > ChiSq
Deviance	0.0000	0	.	.
Pearson	0.0000	0	.	.

Number of events/trials observations: 6

Model Fit Statistics

Criterion	Intercept Only	Intercept and Covariates	With Constant
AIC	4390.699	3831.344	41.525
SC	4398.280	3876.829	87.010
-2 Log L	4388.699	3819.344	29.525

Type 3 Analysis of Effects

Effect	DF	Wald Chi-Square	Pr > ChiSq
group	1	166.2885	<.0001
study	2	4.8685	0.0877
group*study	2	0.1446	0.9303

Analysis of Maximum Likelihood Estimates

Parameter		Est	Std Error	Wald Chi-Sq	Pr>ChiSq
Intercept		-5.5870	0.2089	715.3004	<.0001
group	Control	2.7871	0.2161	166.2885	<.0001
study	Harper	-0.4355	1.0223	0.1815	0.6701
study	Koutsky	0.9155	0.4334	4.4626	0.0346
group*study	Control*Harper	0.2773	1.0505	0.0697	0.7918
group*study	Control*Koutsky	0.1340	0.4489	0.0891	0.7653

Reduced Model
(Corresponding values)

Criterion	Value	DF	Value/DF	Pr > ChiSq
Deviance	0.1500	2	0.0750	0.9278
Pearson	0.1453	2	0.0726	0.9299

Criterion	Intercept Only	Intercept and Covariates	With Constant
AIC	4390.699	3827.494	37.675
SC	4398.280	3857.817	67.998
-2 Log L	4388.699	3819.494	29.675

Effect	DF	Wald Chi-Square	Pr > ChiSq
group	1	230.4406	<.0001
study	2	88.2082	<.0001

Parameter		Est	Std Error	Wald Chi-Sq	Pr>ChiSq
Intercept		-5.6258	0.1826	949.5308	<.0001
group	Control	2.8285	0.1863	230.4406	<.0001
study	Harper	-0.1748	0.2351	0.5528	0.4572
study	Koutsky	1.0403	0.1127	85.1311	<.0001

Table 7. Edited SAS output for the loglinear model analysis for HPV 16 infection, saturated and reduced models.

Saturated Model

The GENMOD Procedure

Model Information
Distribution   Poisson
Link Function   Log

Number of Observations Read 12
Number of Observations Used 12

Class Level Information

Class	Levels	Values
group	2	Control Vaccine
event	2	No Yes
study	3	Harper Koutsky Patricia

Criteria For Assessing Goodness Of Fit

Criterion	DF	Value	Value/DF
Deviance	0	0.0000	.
Full Log Likelihood		-41.6041	

LR Statistics For Type 3 Analysis

Source	DF	Chi-Square	Pr > ChiSq
group	1	138.29	<.0001
event	1	5835.45	<.0001
group*event	1	164.35	<.0001
study	2	352.68	<.0001
group*study	2	0.04	0.9796
event*study	2	14.38	0.0008
group*event*study	2	0.15	0.9278

Reduced Model
(Corresponding values)

Criterion	DF	Value	Value/DF
Deviance	4	2.1689	0.5422
Full Log Likelihood		-42.6886	

Source	DF	Chi-Square	Pr > ChiSq
group	1	417.37	<.0001
event	1	5901.76	<.0001
group*event	1	493.83	<.0001
study	2	1821.77	<.0001
event*study	2	73.94	<.0001

Acknowledgments

REFERENCES

Barat, C. E., Wright, C., and Chou, B. (2011), "Examining Potential Predictors for Completion of the Gardasil Vaccine Sequence Based on Data Gathered at Clinics of Johns Hopkins Medical Institutions," *Journal of Statistics Education*, 19, available at http://www.amstat.org/publications/jse/v19n1/barat.pdf.

Bednarczyk, R. A., Davis, R., Ault, K., Orenstein, W., and Omer, S. B. (2012), "Sexual Activity-Related Outcomes After Human Papillomavirus Vaccination of 11- to 12-Year-Olds," *Pediatrics*, 130 798–805.

Brown, D.R., Kjaer, S.K., Sigurdsson, K., Iversen, O.E., Hernandez-Avila, M., Wheeler, C.M., Perez, G., Koutsky, L.A., Tay, E.H., Garcia, P., and et al. (2009), "The Impact of Quadrivalent Human Papillomavirus (HPV; Types 6, 11, 16, and 18) L1 Virus-Like Particle Vaccine on Infection and Disease Due to Oncogenic Nonvaccine HPV Types in Generally HPV-naive Women Aged 16–26 Years," *The Journal of Infectious Diseases*, 199, 926–935.

Centers for Disease Control and Prevention (2012a), "Human Papillomavirus (HPV), 2012a. URL http://www.cdc.gov/hpv. Accessed on November 10, 2012.

——— (2012b), "HPV Vaccine Information for Clinicians—Fact Sheet," available at http://www.cdc.gov/std/hpv/stdfact-hpv-vaccine-hcp.htm. Accessed on November 10, 2012.

City of Toronto (2012), "Human Papillomavirus (HPV) Vaccine for Grade 8 Girls," available at http://www.toronto.ca/health/cdc/factsheets/hpv_vaccine_factsheet.htm. Accessed on November 10, 2012.

Freedman, D., Pisani, R., and Purves, R. (2007), *Statistics* (4th ed.), New York: W.W. Norton & Company, Inc.

Gerson, J. (2012) "Calgary Bishop's HPV Vaccine Ban Putting Thousands of Girls at Risk: MDs," *National Post*, June 26, 2012. Available at http://news.nationalpost.com/2012/06/26/187783. Accessed on November 10, 2012.

Kahn, J. A., Brown, D. R., Ding, L., Widdice, L. E., Shew, M. L., Glynn, S., and Bernstein, D. I. (2012), "Vaccine-Type Human Papillomavirus and Evidence of Herd Protection After Vaccine Introduction," *Pediatrics*, 130, e249–e256.

Lu, B., Kumar, A., Castellsagué, X., and Giuliano, A. R. (2011), "Efficacy and Safety of Prophylactic Vaccines Against Cervical HPV Infection and Diseases Among Women: A Systematic Review & Meta-analysis," *BMC Infectious Diseases*, 11. Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3034689. Accessed on November 9, 2012.

Matthews, J.N.S., and Altman, D. G. (1996), "Interaction 2: Compare Effect Sizes not *P* Values," *BMJ*, 313, 808.

National Cancer Institute (2011), "Cancer Vaccines," available at http://www.cancer.gov/cancertopics/factsheet/Therapy/cancer-vaccines. Accessed on November 10, 2012.

Physicians' Health Study (2009), Physicians' Health Study I, 2009. Available at http://phs.bwh.harvard.edu/phs1.htm. Accessed on November 9, 2012.

WHO/ICO Information Centre on HPV and Cervical Cancer (2012), "United States of America Human Papillomavirus and Related Cancers," Fact Sheet 2010, 2010b. Available at http://apps.who.int/hpvcentre/statistics/dynamic/ico/country_pdf/USA_FS.pdf. Accessed on November 10, 2012.

——— (2012), Statistics, 2010a. Available at http://who.int/hpvcentre/statistics/en. Accessed on November 10, 2012.

World Health Organization (2012), Report of the HPV Vaccine Delivery Meeting: Identifying Needs for Implementation & Research, 17–19 April 2012. 2012. URL http://apps.who.int/iris/bitstream/10665/76532/1/WHO_IVB_12.09_eng.pdf. Accessed on November 9, 2012.

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