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

Alison L. Gibbs and Emery T. Goossens

Department of Statistical Sciences
University of Toronto

alison.gibbs@utoronto.ca and *emery@utstat.toronto.edu*

JSE Webinar
March 18, 2014

A Real World Application

- Why are clinical trials of HPV vaccines a good case study for teaching statistics?
- Clinical trials provide a real world example of statistics in practice.
- HPV and the vaccinations thereof are an important issue that many of today's students can personally relate to.
- While many students may be aware that statistics are used in clinical trials, this case study can be used as an illustration of introductory to intermediate statistical methods as well as drive home their importance.

Statistical Significance

- Data are from a meta-analysis of clinical trials, each of which is an example of an experimental study.
- Thus we have a practical example of a setting with the ability to make casual conclusions.
- Considering a number of related, but different, clinical trials emphasizes the inherent randomness of the data collection process.
- As some of the clinical trials may be considered as follow up studies, students can grapple with the idea that the result of initial studies may very well need to be verified many times over, depending on the application.

The Data

- The data we use in this case study are taken from a meta-analysis of the effectiveness of HPV vaccines in clinical trials.
- The data are from the article "Efficacy and Safety of Prophylactic Vaccines Against Cervical HPV Infection and Diseases Among Women: A Systematic Review and Meta-analysis" (Lu et al., 2011).
- The data come from seven randomized controlled trials of HPV vaccines. The data are given in the form of contingency tables in the original paper. We consider data from four of these trials.

Methods

- Data come in 2×2 contingency tables (control or vaccine group, acquired infection or did not).
- Some of the contingency tables can be combined.
- Variety of methods are appropriate:
  - inference for two proportions
  - chi-square test of homogeneity
  - randomization tests
  - Fisher's exact test
  - multinomial likelihood ratio test
  - logistic regression
  - log-linear models (Poisson regression)
  - odds ratio and relative risk or vaccine efficacy
  - meta-analysis
- Creates opportunities for discussion of a variety of statistical issues.

Research Questions:

1. Does the HPV vaccine provide protection against the types of HPV for which it was designed?
2. Does it also provide protection against infection with other types of HPV?

Research Question 1: HPV 16 data

Harper et al. study

Group	infection? No	Yes
Control	366	19
Vaccine	413	1

Koutsky et al. study

Group	infection? No	Yes
Control	639	111
Vaccine	748	7

PATRICIA study

Group	infection? No	Yes
Control	5673	345
Vaccine	6140	23

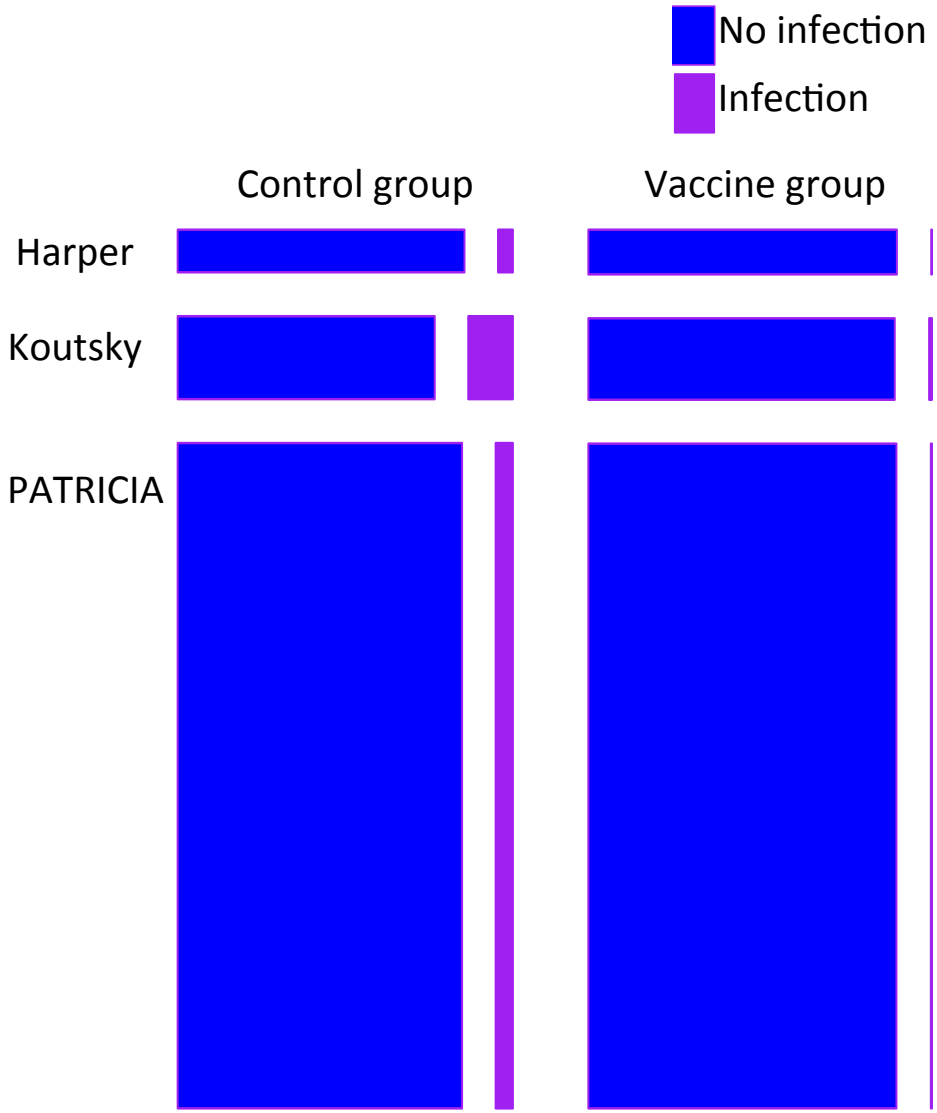
$p < 0.0001$

Discussion

Effect of small sample size

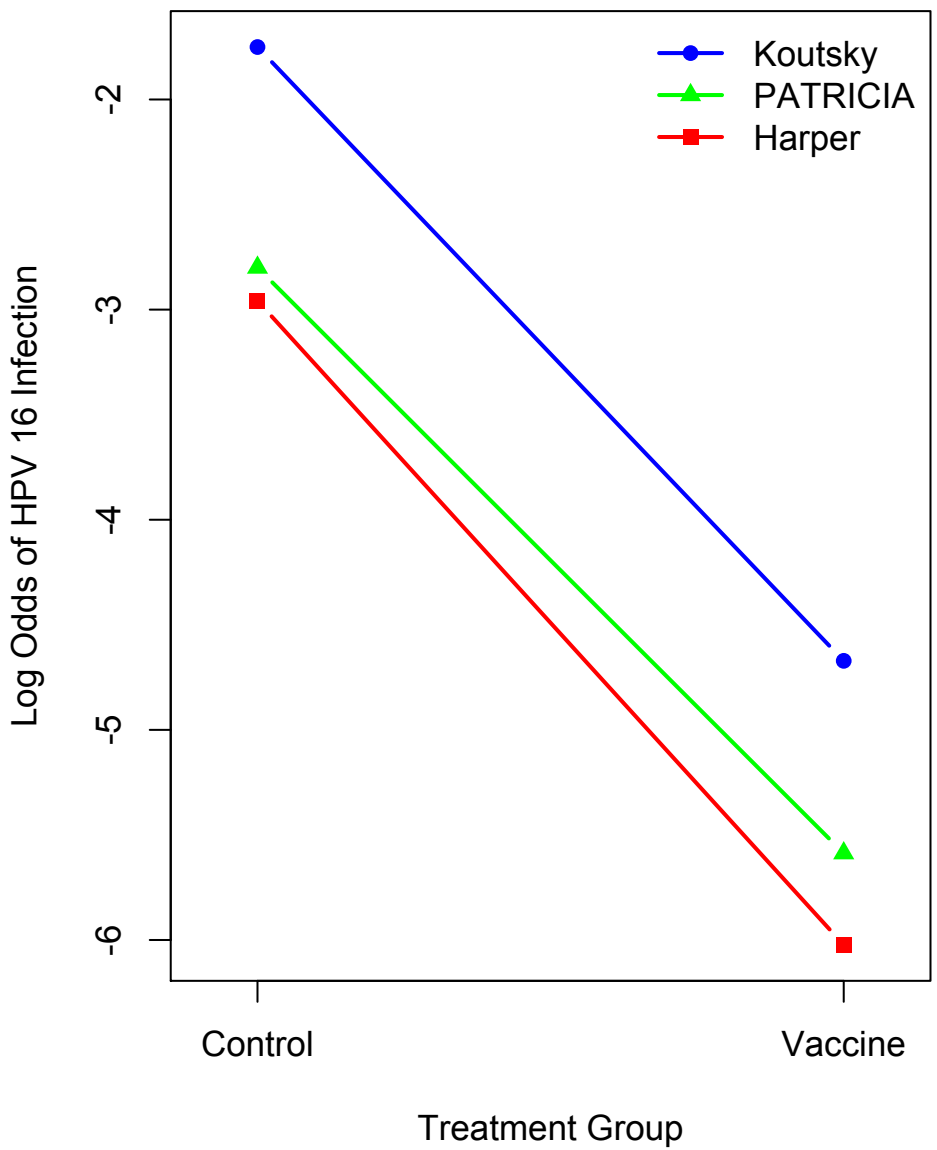
Largest difference in $\hat{p}_{infected}$

Strongest evidence



Investigating differences across studies

- 2 treatment groups $\times$ 2 outcomes $\times$ 3 studies
- For control group only, (2×3 table): strong evidence ($p < 0.0001$) of different infection rates across studies.
- For treatment group only: only very weak evidence ($p = 0.07$) of different infection rates across studies.
- Does this mean the treatment vs control comparison is different across studies?
- No #1: using log-linear models ($2 \times 2 \times 3$ table), there is no evidence of a 3-way interaction ($p = 0.9$).
- No #2: using logistic regression, there is no evidence of a treatment-study interaction ($p = 0.9$).



Research Question 2: Other types of HPV

Is there evidence of protection against infection with types of HPV that aren't in the vaccine?

FUTURE I study

HPV 31

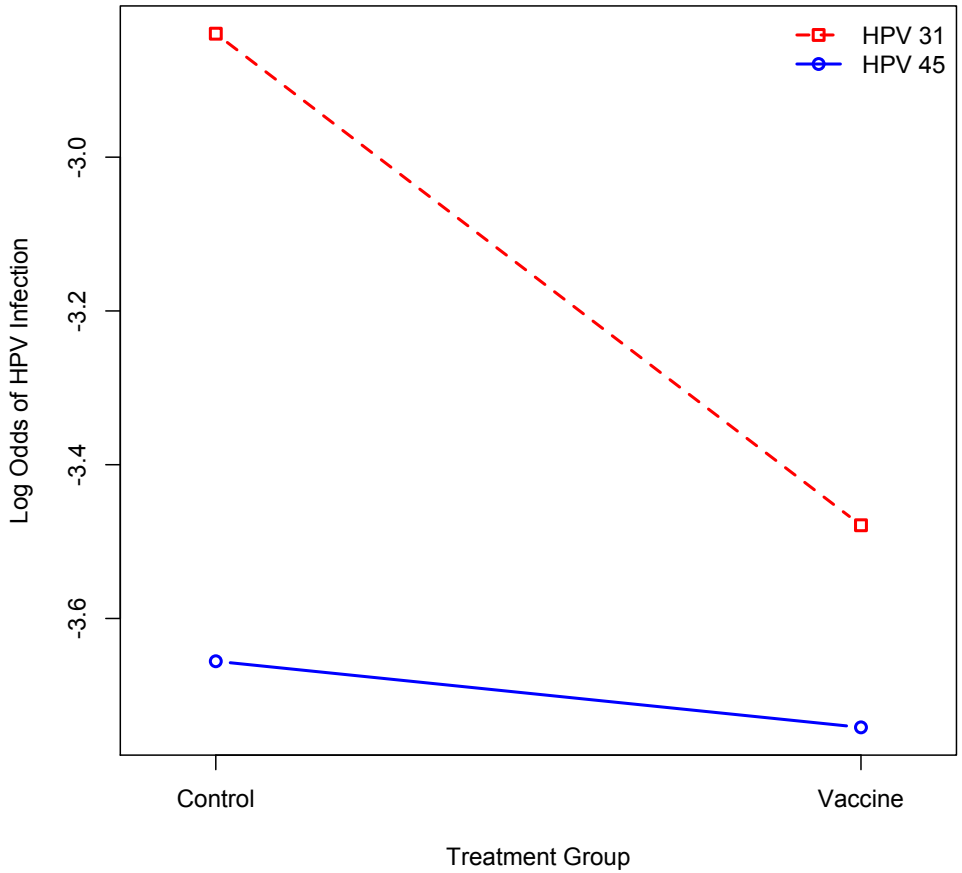
Group	infection? No	Yes
Control	975	57
Vaccine	1005	31

$p = .004$

HPV 45

Group	infection? No	Yes
Control	1006	26
Vaccine	1012	24

$p = .76$



Other types of HPV

Is there evidence of protection against infection with types of HPV that aren't in the vaccine?

	HPV 31		HPV 45	
	infection?		infection?	
Group	No	Yes	No	Yes
Control	975	57	1006	26
Vaccine	1005	31	1012	24

Is there evidence that the difference in the infection rate between the control and vaccine groups is not the same for HPV 31 and HPV 45?

Why can't we carry out this analysis?

The HPV 31 and HPV 45 tables include the same subjects, and some might have become infected with both types of HPV.

Added Context

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, & North, South & Central America)	16 (from Asia-Pacific region, Europe, & North, South & Central America)

Concluding Remarks

- Clinical Trials: Relevant and Real
- Studying statistics matters!
- One story, many data sets.
- Test of equal proportions, contingency table analysis, log-linear models, oh my!
- What does the context add to the discussion?

References

A. Gibbs and E. Goossens (2013). The Evidence for Efficacy of HPV Vaccines: Investigations in Categorical Data Analysis. *Journal of Statistics Education* **21**(3). Available at http://www.amstat.org/publications/jse/v21n3/gibbs.pdf.

B. Lu, A. Kumar, X. Castellsagué, and A. Giuliano (2011). Efficacy and Safety of Prophylactic Vaccines Against Cervical HPV Infection and Disease Among Women: A Systematic Review & Meta-analysis. *BMC Infectious Diseases* **11**. Available at http://www.biomedcentral.com/1471-2334/11/13.