HIV Vaccine Clinical Trials

After completing this section, students should be able to:

• Explain why clinical trials use placebos.
• Interpret a p-value.
• Read the article “AIDS vaccine promising; experts urge caution” from SF Gate Sept 25, 2009.

• Read the article “Another H.I.V. Vaccine Fails a Trial, Disappointing Researchers” from the NYTimes, Feb 4, 2020.

• Answer the questions:

1. The 2009 SF Gate Article “AIDS vaccine promising; experts urge caution” says that: “Of the 8,197 volunteers who were given the vaccine, new infections occurred in 51 people. New infections occurred in 74 of 8,198 participants who received the placebo shot.” It also states that “the vaccine regimen was safe and 31 percent effective in preventing HIV infection compared with a placebo.” Where does the 31 percent figure from?

   (a) 74 is 31% higher than 51
   (b) 51 is 31% lower than 74
   (c) 74 is 31% of the total number of cases
   (d) 51 is 31% of total cases

2. In the HIV vaccine trial, half the participants given placebos, and the participants didn’t know if they received the real vaccine or the placebo. If this hadn’t
been done, and participants knew whether or not they had received a vaccine, how might this have altered the results of the trial? Select all that apply.

(a) The people who knew they did not receive the vaccine might have used condoms more conscientiously, causing the vaccine to look less effective than it is.

(b) The people who knew they did not receive the vaccine might have used condoms more conscientiously, causing the vaccine to look more effective than it is. Feedback: If people without the vaccine used condoms more conscientiously, then people without the vaccine might have lower incidence of HIV, making it look like the vaccine was LESS effective.

(c) The people who knew they did receive the vaccine might have engaged in sex with more partners, causing the vaccine to look less effective than it is. Feedback: Right, if people with the vaccine had more sex partners, then people with the vaccine would raise their risk of infection, making it look like the vaccine was less effective. There is also another correct answer.

(d) The people who knew they did receive the vaccine might have engaged in sex with more partners, causing the vaccine to look more effective than it is. Feedback: If people with the vaccine had more sex partners, then people with the vaccine would raise their risk of infection, making it look like the vaccine was LESS effective.
3. In the 2009 SF Gate article “AIDS vaccine promising; experts urge caution”, why did experts urge caution? Select all that apply.

(a) The virus didn’t seem to lower the viral load for people who still got infected.
(b) The results of the vaccine might not apply to the US population.
(c) The difference between the number of people who got infected in the treatment group and placebo group might have been due to chance variation, rather than any effect that the vaccine had.
Introduction

In the article “AIDS vaccine promising; experts urge caution” from the San Francisco Chronicle from 9/25/2009, we are told:

Of the 8,197 volunteers who were given the vaccine, new infections occurred in 51 people. New infections occurred in 74 of 8,198 participants who received the placebo shot.

Question. Could this difference be reasonably attributed to chance?
Coin flipping

If you flip a coin 100 times, will you always get exactly 50 head and 50 tails?

Would you be surprised to get 45 heads and 55 tails?

Would you be surprised to get 33 heads and 67 tails? (PollEv)
If you flip a coin 125 times, would you be surprised to get 51 heads and 74 tails? (PollEv)
Coin flipping and the HIV vaccine trial

What does this have to do with the HIV vaccine trial?

Recall, there were 51 new infections among the 8,197 volunteers who were given the vaccine, and 74 new infections among the 8,198 participants who received the placebo shot.
Difference in proportions

Here is another, more standard approach to analyzing the probability of getting the HIV vaccine result by chance.

Recall, there were 51 new infections among the 8,197 volunteers who were given the vaccine, and 74 new infections among the 8,198 participants who received the placebo shot.

What proportion of people got HIV infections in the vaccination arm of the trial?

What proportion of people got HIV infections in the placebo arm?

What is the difference in proportions?
What proportion of people got HIV infections among all of the trial participants?
If the vaccine has absolutely no effect, then the trial is like picking people at random out of a group of people, some of whom are destined to get HIV, and putting them in the two groups.

Suppose we have a population in which ______ percent overall got HIV, and we take a sample of 8197 people and a sample of 8198 people at random, and look at the difference in proportions of HIV positive people in those two samples. This is the distribution of differences in proportion we get if we do this over and over again.
Randomization Test for a Difference in Proportions

Null Hypothesis: $p_1 = p_2$

Original Sample

<table>
<thead>
<tr>
<th>Group</th>
<th>Count</th>
<th>Sample Size</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>51</td>
<td>8197</td>
<td>0.0062</td>
</tr>
<tr>
<td>Group 2</td>
<td>74</td>
<td>8198</td>
<td>0.0090</td>
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<tr>
<td>Group 1-Group 2</td>
<td>−23</td>
<td>n/a</td>
<td>−0.0028</td>
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Randomization Sample

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>53</td>
<td>8197</td>
<td>0.0065</td>
</tr>
<tr>
<td>Group 2</td>
<td>72</td>
<td>8198</td>
<td>0.0088</td>
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<tr>
<td>Group 1-Group 2</td>
<td>−19</td>
<td>n/a</td>
<td>−0.0023</td>
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</table>
Here is the output if we ask RStudio to do a test for difference of proportions:

```r
> prop.test(c(51, 74), c(8197, 8198))

  2-sample test for equality of proportions with continuity correction
data:  c(51, 74) out of c(8197, 8198)
  X-squared = 3.899, df = 1, p-value = 0.04831
  alternative hypothesis: two.sided
  95 percent confidence interval:
  -5.589346e-03 -2.026082e-05
  sample estimates:
    prop 1    prop 2
  0.006221788 0.009026592
```

The p-value is 0.0481. What does this mean?
The NYTimes article is about a subsequent trial in South Africa on the same vaccine.

A Feb 3 National Institute of Health (NIH) report states:

In the January 23, 2020 interim analysis, the DSMB [Data and Safety Monitoring Board] examined data from 2,694 volunteers who received the investigational vaccine regimen and 2,689 volunteers who received the placebo injection. ... In this analysis, 129 HIV infections occurred among the vaccine recipients, and 123 HIV infections occurred among the placebo recipients.

What do you think is the best interpretation of this result? (PollEv)

A. The vaccine works.
B. The vaccine makes it more likely to get HIV.
C. The vaccine doesn’t have any effect on contracting HIV.
Di erence in proportions

Randomization Test for a Difference in Proportions

Randomization Dotplot of \( p_1 - p_2 \)  Null Hypothesis: \( p_1 = p_2 \)

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</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>129</td>
<td>2694</td>
<td>0.048</td>
</tr>
<tr>
<td>Group 2</td>
<td>123</td>
<td>2689</td>
<td>0.046</td>
</tr>
<tr>
<td>Group 1-Group 2</td>
<td>6</td>
<td>n/a</td>
<td>0.0021</td>
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Randomization Sample

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<th>Sample Size</th>
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<tr>
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<td>0.049</td>
</tr>
<tr>
<td>Group 2</td>
<td>121</td>
<td>2689</td>
<td>0.045</td>
</tr>
<tr>
<td>Group 1-Group 2</td>
<td>10</td>
<td>n/a</td>
<td>0.0036</td>
</tr>
</tbody>
</table>

> prop.test(c(129, 123), c(2694, 2689))

2-sample test for equality of proportions with continuity correction

data:  c(129, 123) out of c(2694, 2689)
X-squared = 0.094562, df = 1, p-value = 0.7585
alternative hypothesis: two.sided
95 percent confidence interval:
-0.009514968  0.013799519
sample estimates:
prop 1  prop 2
0.04788419  0.04574191
How do you make sense of these two clinical trials of the same vaccine, one that showed an effect and one that did not?
Homework

1. There is some evidence that the BCG vaccine for tuberculosis can also offer protection against other respiratory infections, and therefore might be worth investigating as a way to increase people’s resistance to coronavirus – several clinical trials are currently investigating this possibility. The evidence comes from past studies, including a study published in 2013 “Acute Lower Respiratory Infection Among Bacille Calmette-Guérin (BCG)–Vaccinated Children” in the Journal of the American Academy of Pediatrics. This study followed children who did and did not receive BCG and tracked incidence of pneumonia. The study found that of the 55928 children in the vaccinated group, there were 8299 who got acute lower respiratory infection (ALRI), while in the 2093 children in the non-vaccinated group, there were 383 who got ALRI.

(a) What proportion of the children in the vaccinated group got ALRI? (your answer should be a decimal or a percent)

(b) What proportion of the children in the non-vaccinated group got ALRI? (your answer should be a decimal or a percent)

(c) What is the difference in proportions? (your answer should be a decimal or a percent)

(d) Based on this StatKey distribution for difference in proportion, which the num-
bers from the study, is it likely to observe this big a difference in proportions in two samples just by chance? Explain.

(e) Use R Studio to get a p-value for the difference in proportions. Recall, in the class notes this was done with the command `prop.test(c(51, 74), c(8197, 8198))` for the 2009 HIV vaccine trial. Use a similar command. Write your answer as a decimal.

(f) Based on your answer to part (e), is it likely to see this kind of difference in proportion just by chance?

(g) The study of the BCG vaccine was not a randomized controlled trial, but an observational study. That means, the children were not divided by a random process in to the vaccine and non-vaccine group (and no placebo was used). So there may be other differences between the two groups that could explain the
lower incidence of ALRI besides the BCG vaccine. Give at one way in which the vaccinated group could plausibly be different from the non-vaccinated group that could contribute to the vaccinated group having a lower incidence of ALRI (even if the vaccine isn’t having an effect on ALRI incidence).

2. A (pretend) clinical trial on a new drug in patients with sunburn showed a statistically significant improvement (p-value 0.03). What does this number mean? Select the best answer.

(a) 97% of the patients in the treatment group were helped by the drug
(b) the drug resulted in a 3% improvement in the treatment group compared to the control group
(c) if the drug has no effect, you would expect as extreme a difference between the treatment group and the control group 3% of the time
(d) there is a 3% chance that the the drug is not effective