Chapter 12: Comparing Risk (STAT 212 Only)

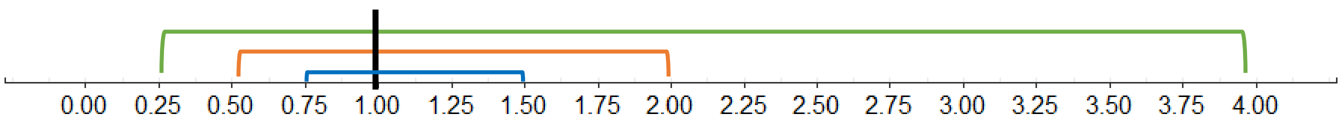
Inference for Risk Comparison

- Reviewing Risk

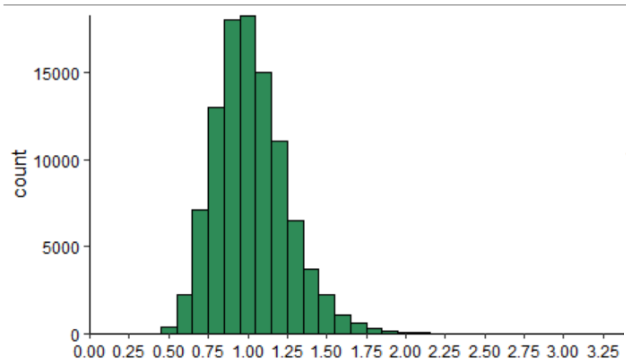
Example: Recall this example, where children were given the "Salk" vaccine for polio or a placebo injection. The following data shows how many children in each group developed polio.

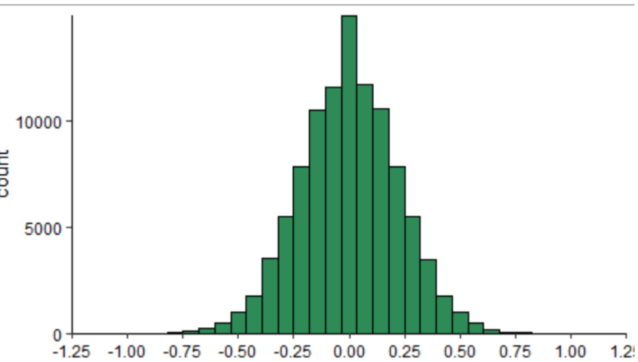
	Polio	No Polio	Total
Salk Vaccine	33	200,712	200,745
Placebo	115	201,114	201,229

- **Confidence Intervals** for Relative Risk (RR)
  - Fundamentally, we're doing what we've done before—calculate the standard error for RR and extend out a certain distance to capture where the true RR <u>parameter</u> could be.
  - What makes this trickier for RR is that it is an exponentially-scaled measure.



  - However, the logarithm of the distribution of possible RR's will be symmetrically distributed!
    - The distribution on the left represents the sampling distribution for $\widehat{RR}$ when the true parameter RR = 1 (n_1 = 100, n_2 = 100)
    - The distribution on the right represents the sampling distribution for the log($\widehat{RR}$) when RR = 1 (n_1 = 100, n_2 = 100)





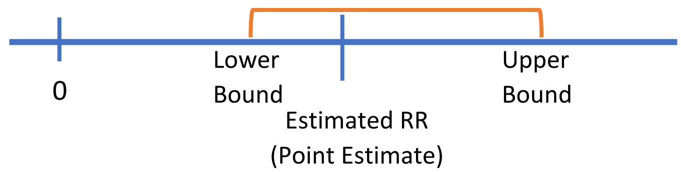
  - By finding a confidence interval for log($\widehat{RR}$), and then converting back, we have a confidence interval that works!

> $\log(\widehat{RR}) \pm z^* SE_{\log(\widehat{RR})}$ *...which after taking the exponent of both sides is...* $\widehat{RR} \pm e^{z^* SE_{\log(\widehat{RR})}}$

Make note that we won't do this by hand! Just good to have awareness of how this works

- **The confidence interval will be <u>assymmetric</u>** about the point estimate—which might feel strange, but appropriately reflects the Relative Risk scale.
- For our class, we will not calculate this value by hand. We will focus on *interpreting* a confidence interval and use an online calculator https://www2.ccrb.cuhk.edu.hk/stat/confidence%20interval/CI%20for%20relative%20risk.htm

Asymmetric Confidence Interval



Practice: Let's try out this calculator by calculating the 95% confidence for the relative risk of the Salk Vaccine group.

Using your confidence interval for RR, report the 95% confidence interval for the Salk Vaccine's effectiveness.

Practice: In the Salk Vaccine study, the relative risk was 0.2876. A 95% confidence interval for *<u>relative risk</u>* is calculated to be (0.196, 0.424). Which of the following statements correctly interprets this interval?

1) We are 95% confident that the risk for contracting polio for those who had the salk vaccine is between 19.6% and 42.4% of the risk for contracting polio for those without the vaccine.

2) We are 95% confident that the incidence rate for polio is 19.6% with the salk vaccine and 42.4% without the vaccine.

3) We are 95% confident that the risk for polio is between 19.6% and 42.4% lower for those who had the salk vaccine as compared to without the vaccine.

- **Hypothesis testing** for Risk Comparison
  - To determine if the intervention of interest is truly changing risk, we might be interested to directly test for a difference.
  - The simplest way is to complete a test for two proportions, where H_0: $p_1 = p_2$.
  - We won't complete this computation by hand either, but we will learn to identify the null and alternative hypotheses and interpret the p-value.

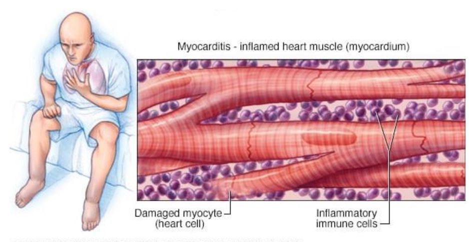
Computational Background for comparing proportions (no calculations by hand)

$$z = \frac{\hat{p}_1 - \hat{p}_2}{SE_{\hat{p}_1 - \hat{p}_2}} \qquad \text{where} \qquad SE_{\hat{p}_1 - \hat{p}_2} = \sqrt{\hat{p}(1-\hat{p})(\frac{1}{n_1} + \frac{1}{n_2})}$$

Practice: The COVID-19 mRNA vaccines (Pfizer and Moderna) have been shown to result in a slight increased risk for myocarditis/pericarditis (an inflammation of the heart muscle that can affect the heart's ability to pump blood). This risk is most pronounced among younger people (ages 12-24).

Using all data collected by June 11, 2021, the CDC reported the following, showing total injections administered in the U.S. of these two vaccines, and total cases reported at that time.
https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-06/05-COVID-Wallace-508.pdf

Group and sample size	Cases reported
Males (n = 6,377,158)	347
Females (n = 7,426,988)	42



What is the relative risk for myocarditis/pericarditis for males as compared to females?

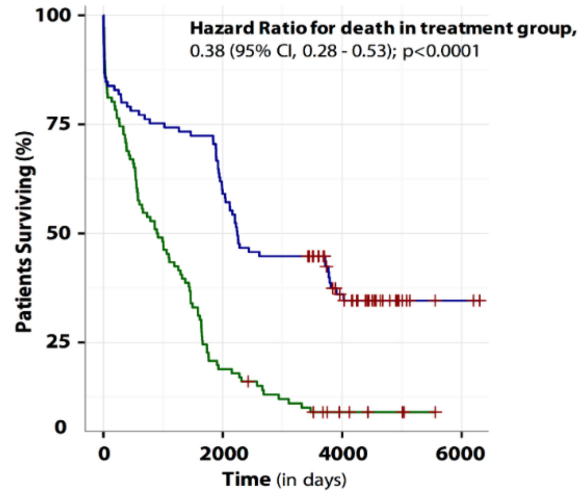
The p-value from a 2-sample proportions test is very tiny (around 1×10^{-20}). What should we conclude from this result?

If we were to complete a 95% confidence interval for the true relative risk of myocarditis/pericarditis among males in comparison to females, would you expect this interval to overlap 1? Why or why not?

Hazard Ratio and Survival Curves

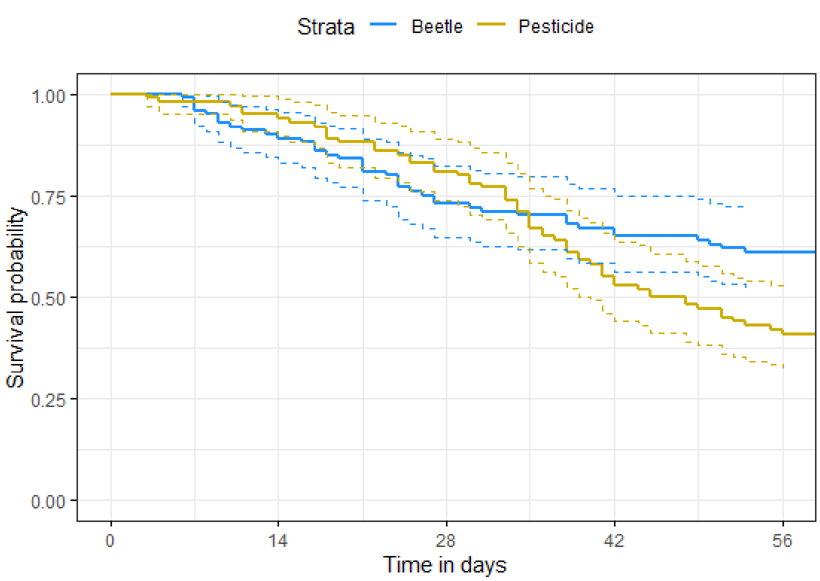
- What is a Hazard Ratio?
  - The hazard ratio is quite similar to relative risk, but with one additional element added. It can be calculated to find the relative risk over a time range.
  - We will **not** calculate hazard ratios by hand in our class.

- Survival Curves (Kaplan-Meier Plots)
  - Kaplan-Meier plots are common ways to represent risk comparisons across time.
  - The groups in question are each represented with a line, and the y axis represents probability still uninfected/alive at each time point.
  - Some curves *may* also include markers to identify when patients are "censored" from the study
    - Patients drop out, or they joined late and cannot be observed for length of study. These situations require additional analytical methods that we will forego in this class



Albarqouni (2016)

Practice: Botanists are trying to stop plant damage due to Western Flower Thrips, a plant-eating bug that rots the plant. The new Treatment is to embed the natural predator Rove Beetle and the standard treatment is to use the standard pesticide. 200 plants are randomly assigned to each treatment.

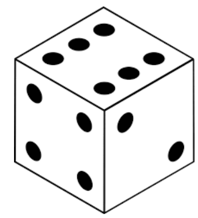


David Cappaert, bugwood.org

Based on this plot, how would you describe the effectiveness of each treatment over time?

Calculating "Odds" (when Risk cannot be directly assessed)

- What are Odds?
  - "Odds" is another measure of risk that is commonly found in medical studies. They are useful in cases where we **don't** have natural incidence sampling from the population.
  - First, let's explore how odds are calculated.
- Comparing Odds vs. Risk/probability
  - If I asked you, what is the probability of rolling a 6 with a six-sided die, how would we calculate that? <u>1/6</u>



  - This calculation is exactly how we calculate risk. It's number of possibilities for this outcome of interest, divided by the total number.
  - But the term "odds" in probability has a very specific meaning. If I asked what are the odds of rolling a 6 with a six-sided die, we would take the probability of rolling a 6 divided by the probability of NOT rolling a 6.

$$\textbf{Formula: Odds} = \frac{P(A)}{P(A^C)} \approx \frac{\#\text{ Cases with}}{\#\text{ Cases without}}$$

  - While we can report odds as a decimal, it's also common to report as a direct comparison:
    - The odds of rolling a six are 1 to 5…or…The odds of avoiding six are 5 to 1
- **Calculating an "Odds Ratio" for comparison in two groups – *Abbreviated OR***
  - In previous examples, we used relative risk (also called "risk ratio") as a common way to directly compare the risks of two populations in the form of a ratio:

	Polio	No Polio	Total
Salk Vaccine	33	200,712	200,745
Placebo	115	201,114	201,229

The estimated RR for polio with the Salk vaccine is $\frac{33/200{,}745}{115/201{,}229}$ = 0.28765

  - We could similarly calculate an "odds ratio" by doing the same thing, but with the odds of contracting polio for each group being directly compared as a ratio:

$$\textbf{Formula: OR} = \frac{Odds_A}{Odds_B}$$

The estimated OR for polio with the Salk vaccine is $\frac{33/200{,}712}{115/201{,}114}$ = 0.28753

  - **Interpreting an Odds Ratio:** The estimated odds of getting polio after taking the Salk Vaccine, as compared to taking the placebo are 0.28753 to 1.

- **When to use an Odds Ratio**
  - When we **don't** have natural incidence sampling of the condition of interest. This typically the situation with Case-Control Studies
  - In experiments, and other observational study designs, RR is preferred as the more straightforward measure.

The data on the left represents a cohort study with 200 women who had a potential "risk factor" gene, and 200 without. The researchers followed up later to see who had ovarian cancer.	The data on the right is a case-control study, where the researchers identified 200 patients who had ovarian cancer and 200 who didn't. Then the researchers looked to see if they also had this gene.

	Ovarian Cancer	No Ovarian Cancer	Totals
Gene	15	185	**200**
No Gene	1	199	**200**
Totals	**16**	**384**	**400**

	Ovarian Cancer	No Ovarian Cancer	Totals
Gene	172	46	**218**
No Gene	28	154	**182**
Totals	**200**	**200**	**400**

Risk: https://www2.ccrb.cuhk.edu.hk/stat/confidence%20interval/CI%20for%20relative%20risk.htm

Report the Relative Risk and CI for data on left	*Report the Relative Risk and CI for data on right*

Odds: https://www2.ccrb.cuhk.edu.hk/stat/confidence%20interval/CI%20for%20ratio.htm

Report the Odds Ratio and CI for data on left	*Report the Odds Ratio and CI for data on right*

Summarizing use of Odds Ratios

- ✓ In low incidence situations, you need very large samples to detect effects
- ✓ Case-control designs are an efficient option that doesn't require an *enormous* sample size.
- ✓ In case-control designs, RR cannot be calculated accurately. But OR can be validly measured
- ✓ An OR will always exaggerate the effect in comparison to relative risk, but the **larger the sample size**, the closer OR will be in approximating RR.
  - ▪ RR will always be closer to __
- o An OR is still valid in other designs, but RR is preferred when appropriate.

- **Inference for Odds Ratios**
  - o Just as with Relative risk, our samples only yield sample statistics. We can again complete confidence intervals or hypothesis tests to make an inference.

Practice: A research article appearing in the *American Journal of Obstetrics and Gynecology* published findings on the association between marijuana use and pregnancy-related issues. The researchers completed a Case-Control Study to examine the records of 12,069 pregnancies. The following 5 outcomes were higher for marijuana-users as compared to non-marijuana users.

Possible Outcomes	Odds Ratio and 95% CI	P-value from HT
Maternal-related Asthma	3.30 (1.52, 7.17)	0.003
2 or more mental health issues	5.97 (3.01, 10.78)	<0.001
Head circumference <25th percentile	1.44 (0.82, 2.53)	0.202
Birthweight <25th percentile	1.09 (0.61, 1.95)	0.763
Hypertension	1.30 (0.68, 2.50)	0.42

Which outcome did marijuana seem to elevate most?

Which outcomes are we not as confident in concluding are truly higher for the marijuana group?

Would it be correct to say that the odds for hypertension are estimated to be 1.30x *higher* for women who in the marijuana group as compared to the non-marijuana group? Why or why not?

Practice: A study was conducted to examine the effectiveness of an experimental brain stimulation treatment on patients with a traumatic brain injury (TBI). Of 143 patients recovering from TBI, 72 were randomly assigned to a brain stimulation treatment in addition to standard medication while the other 71 were assigned to just the standard medication. Results are shown in the table below showing the mortality rate of patients after 6 months.

	Death	**Survival**	**Totals**
Brain Stimulation	21	51	72
Standard Medication	28	43	71

Estimate the relative risk for death for those in the brain stimulation intervention relative to the standard medication intervention.

The 95% confidence interval for relative risk is calculated to be (0.466, 1.170). What does this tell you about how confident we are in the brain stimulation treatment being better at preventing death?

Based on how this study was conducted, should we calculate odds ratios instead, or is relative risk an appropriate measure here?