STATISTICS 305/605: Intro to Biostatistics

September 22, 2021

Lecture 9: Measures of Association in 2x2 Tables

(Reading: PB Section 6.5)

1 Goals of Lecture

- When we look at data in a 2×2 table, we often want to quantify the relationship between the variables
- In the past we have compared differences between probabilities for one variable at different levels of the other variable
- We will look now at *ratios* between probabilities and a related quantity, odds.
  - It turns out that ratios measure associations between variables better than differences.
- We can use these measures to quantify risks.

2 Association in 2×2 tables

- Measures of ASSOCIATION measure the strength of a *relationship* between two variables
- We consider a situation where there are two groups on which a binary variable Y is measured
  - The "groups" can be represented by another binary variable, say X
  - Separate probabilities of success, p_1 and p_2 for each group
    - These are the same as *conditional probabilities that* $Y = 1$ *given* $X = 1$ *or* $X = 2$, *respectively!*

- "Association" in this context means that these conditional probabilities of success are different for the two groups.
    - We want to compare p_1 and p_2
- *For example, is hospitalization with Covid associated with vaccine status?*
    - *Vaccine status (X) forms several groups, but we can focus on fully vaccinated vs. non vaccinated, and measure Y=hospitalization status on members of each group*
    - *Is conditional probability of hospitalization the same for each vaccine group?*

- We have previously compared two probabilities by taking differences, $p_1 - p_2$

- Not ideal: the interpretation of a difference in probability depends on the magnitude of the two probabilities
    - With moderate or large probabilities, a small difference in probability, $p_1 - p_2$, is practically meaningless
    - With small probabilities (rare events) *all* differences are small in magnitude, even when they are extremely important
    - *If Covid vaccines decrease your chance of getting Covid on an airplane with an infected passenger from .510 to .501, the difference in probability is 0.009, but the utility of the vaccine is negligible*
    - *If, instead, the shot reduces your chance from 0.010 to 0.001, then this difference is also 0.009, but represents a 90% reduction*

- We need alternative comparisons to use, instead of differences, that provide more meaningful comparisons for small probabilities

3 Relative Risk

- The RELATIVE RISK is defined as the ratio of two probabilities, $RR = p_1/p_2$ (assuming $p_2 \neq 0$)
    - Measures the multiplicative change in probability of success of numerator group, *relative* to probability of success in denominator group
    - Probability of success is often called "risk" when "success" is some bad thing
    - $0 \leq RR < \infty$
    - Equal probabilities means $RR = 1$

- In the examples above, the relative risks would be
    - $0.510/0.501 = 1.02$, so the risk of Covid on an airplane without vaccine would be 1.02 times as high (or .02 times higher, or 2% higher) than with it.

Table 1: Covid Hospitalizations vs. Vaccine Status in BC for Aug 7-Sept 6

		Hospitalization		
		Yes	No	Total
Vax Status	Unvax	511	1,399,489	1,400,000
	Vax	77	3,499,923	3,500,000
	Total	588	4,899,412	4,900,000

  - $*$ Could write this the other way: $0.501/0.510 = 0.98$, so Covid risk would be reduced 2% with vaccine, relative to without.
- $0.010/0.001 = 10.0$, so the risk of Covid on an airplane without the shot would be 10 times as high (or 9 times higher or 900% higher) than with it.
  - $*$ Could write this as $0.001/0.010 = 0.1$, so disease risk would be decreased 90% by the vaccine

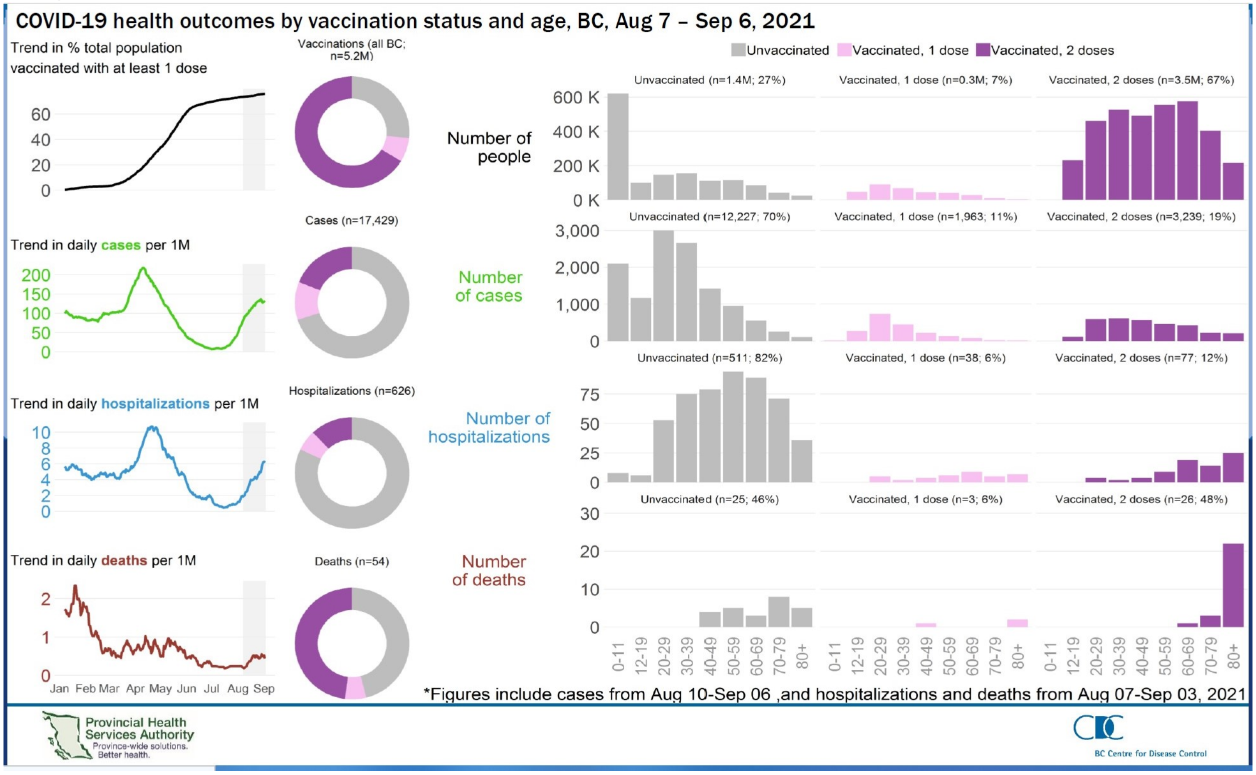
- We estimate relative risk using the sample proportions, $\widehat{RR} = \hat{p}_1/\hat{p}_2$, again assuming $\hat{p}_2 \neq 0$
- We can find a confidence interval for RR, but details are a little complicated
  - Sampling distribution of $\widehat{RR}$ tends to be very skew, but normal approximation for $\log(\widehat{RR})$ works pretty well
  - Make CI in log scale and exponentiate results, like we did for mean of PSA in Lecture 3
  - Best CI has complicated formula (see STAT 475) but can be computed in R

EXAMPLE: Covid Hospitalization vs. Vaccination Status in BC (Lecture 9 scripts.R) We once again turn to weekly data on Covid in BC, as posted on the BC CDC Website. This time we take the weekly data summary from September 9 (the most recent at this writing), located here, and covering the 1-month period from Aug 7, 2021 to Sept 6, 2021. The data we need are sort of in Figure 1. The series of histograms on the right show total population size, cases, hospitalizations, and deaths from the past month, separated by vaccination status. The data we want are in the rows for total population and hospitalization, and in the columns for Unvaccinated and Vaccinated, 2 doses. (We ignore the middle column for now.) The numbers for population size are rounded, but they will work well enough for our purposes. I have extracted them into Table 1.

Perhaps you can see what is going to happen here already, just by looking at the data. There are more hospitalizations in the Unvax group, but there are more people from the rest of the population in the Vax group. So it looks like the Vax group has a reduced risk of hospitalization. But we can quantify this more precisely by calculating the relative risk, starting from the "risk" of hospitalization during the month as the conditional probability of hospitalization, given vaccine status.

I start by entering the data as I have before, then running `xtabs()` to create a table and `prop.table()` to compute conditional probabilities for the two hospitalization levels

Figure 1: BC health outcomes by vaccination status from September 9 Data Summary



for each vaccine status. Letting Group **v** be the Vax group and Group **n** be Unvax, I then compute the risk difference, $\hat{p}_v - \hat{p}_n$ and the relative risk "both ways": $\widehat{RR}_1 = \hat{p}_v/\hat{p}_n$ from which we can quantify decreased risk from the vaccine, and $\widehat{RR}_2 = \hat{p}_n/\hat{p}_v$ from which we can see increased risk from being unvaccinated. One is just the reciprocal of the other, so which way we compute it is just a matter of how we want to express the results.

```
> # Enter the data
> vax.status = rep(x=c("NoVax", "Vax"), each=2)
> hosp.status = rep(x=c("Yes","No"), times=2)
> counts = c(511, 1399489, 77, 3499923)
>
> alldat = data.frame(vax.status, hosp.status, counts)
> alldat
  vax.status hosp.status  counts
1      NoVax         Yes     511
2      NoVax          No 1399489
3        Vax         Yes      77
4        Vax          No 3499923
>
> # xtabs() creates a cross-tabulation using formula=
> #   Left side of formula are the counts
> #   Right side are the variables to form the table, in form
> #     counts ~ row + column
> tbl = xtabs(formula=counts~vax.status + hosp.status, data=alldat)
> tbl
          hosp.status
vax.status      No     Yes
     NoVax 1399489     511
     Vax   3499923      77
>
> # Prop.table() computes conditional probabilities/proportions
> #   using a table as x= and "given" variable as margin=
> (risks = prop.table(x=tbl, margin="vax.status"))
          hosp.status
vax.status        No      Yes
     NoVax 0.999635 0.000365
     Vax   0.999978 0.000022
>
> # Risk *difference*
> risks[2,2] - risks[1,2]
[1] -0.000343
>
> # Relative Risk each way
> risks[2,2]/risks[1,2]
[1] 0.06027397
> risks[1,2]/risks[2,2]
[1] 16.59091
>
> # Confidence intervals using riskscoreci() from PropCIs package
>
> ### install.packages(package=PropCIs)
> library(package=PropCIs)
> # Putting unvax in numerator (row 1 of tbl)
> riskscoreci(x1=tbl[1,2], n1=sum(tbl[1,1:2]),
+             x2=tbl[2,2], n2=sum(tbl[2,1:2]), conf.level=.95)
data:

95 percent confidence interval:
 13.06368 21.07051

> # Putting vax in numerator (row 2 of tbl)
> riskscoreci(x1=tbl[2,2], n1=sum(tbl[2,1:2]),
+             x2=tbl[1,2], n2=sum(tbl[1,1:2]), conf.level=.95)
data:

95 percent confidence interval:
 0.04745969 0.07654812
```

From the table of conditional probabilities of hospitalization given vaccine status, we see that the probability of hospitalization in the Aug 7-Sept 6 period was is very, very low as measured across the total population of BC, but we also see that the conditional probability is rather higher for the unvaccinated group. The first relative risk is $\widehat{RR}_1 = \hat{p}_v/\hat{p}_n = 0.060$, which tells us that vaccinated people have 0.06 times the probability of hospitalization that unvaccinated people do. We can interpret this to mean that vaccine group had a $100 * (1 - 0.060) = 94\%$ lower risk of hospitalization. Next, we find $\widehat{RR}_2 = \hat{p}_n/\hat{p}_v = 16.6$, meaning that unvaccinated people are 16.6 times as likely to be hospitalized with Covid as vaccinated people are. Confidence intervals for these two RR's are (0.047, 0.077) for RR_1 (equivalently, (92.3, 95.3) expressed as percent reduction), and (13.1, 21.2) for RR_2. The tightness of these intervals clearly eliminates the possibility of equal probabilities, $RR = 1$. Either way, there is substantial evidence of a reduced probability of hospitalization among vaccinated people.

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4 Odds Ratios

- Relative risks are *very* useful for comparing small probabilities, like in our example.
- Not as useful for large probabilities, because the range of possible values is very limited
  - If $p_1 = 0.75$, then the minimum possible RR is $0.75/1 = 0.75$
  - if $p_2 = 0.75$, then the maximum possible RR is $1/0.75 = 1.33$
- Also, the sampling distributions of $\widehat{RR}$ and $\log(\widehat{RR})$ have asymmetry that persists unless samples are moderately large, especially when probabilities are small
- The ODDS RATIO (OR) is an alternative comparison that has some better properties for inference
- ODDS OF SUCCESS is defined as $P(\text{Success})/P(\text{Failure}) = p/(1-p)$
- ODDS RATIO is the ratio of the odds of success in group 1 to the odds of success in group 2:
$$OR = \frac{p_1/(1-p_1)}{p_2/(1-p_2)} = \frac{p_1(1-p_2)}{p_2(1-p_1)}$$
  - $0 < OR < \infty$ as long as no probabilities are zero
  - If $p_1 = p_2$ then $OR = 1$
  - Interpretation like RR except referring to *odds* instead of conditional probabilities
    - "The odds of <success> in <group 1> are <OR> times as high as they are in <group 2>"
- As with RR, denominator group is the "baseline" against which the numerator group is compared.

- Note that OR is also the ratio of [relative risk of success] to the [relative risk of failure]:

$$OR = \frac{p_1/p_2}{(1-p_1)/(1-p_2)}$$

  - If success is relatively rare, then $OR \approx RR$

- Estimated from data using counts from a table, which simplifies to

$$\widehat{OR} = \frac{n_{11}n_{22}}{n_{21}n_{12}}$$

  - Multiply counts for success in Group 1 (n_{11}) and failures Group 2 (n_{22})
    - i.e., counts from opposite corners of table
  - Multiply counts in other opposite corners in denominator

- Confidence interval for OR found similar to that for RR

EXAMPLE: Covid Hospitalization vs. Vaccination Status in BC (Lecture 9 scripts.R) Continuing with the hospitalization data from Table 1, we now compute odds ratios. Specifically, we compute two ORs similar to the two RRs we computed before, where the preference of which one to present would depend on whether you want to use vaccinated or unvaccinated status as the baseline. Then $\widehat{OR}_1$ =the odds of hospitalization for vaccinated people relative to those odds for unvaccinated, and $\widehat{OR}_2$ =the odds of hospitalization for unvaccinated people relative to those odds for vaccinated.

Starting with the table of counts, I mimic the $\widehat{OR}$ formula using counts as given above. Then I calculate 95% CIs for each OR using the `orscoreci()` function, which takes the same arguments as the `riskscoreci()` function we used for RR.

```
> # Recall data table
> tbl
          hosp.status
vax.status      No     Yes
     NoVax 1399489     511
     Vax   3499923      77
>
> # Relative Risk each way:
> #  NOTE ORDER OF COUNTS IN TABLE TO GET THE INDEXES RIGHT!
> #  1 is odds of hosp for vax relative to novax
> #     (Yes,Vax)(No,Novax) / (Yes,Novax)(No,Vax)
> #  2 is odds of hosp for novax relative to vax
> #     (Yes,Novax)(No,Vax) / (Yes,Vax)(No,Novax)
> #
> (OR1 = (tbl[2,2]*tbl[1,1])/(tbl[2,1]*tbl[1,2]))
[1] 0.0602533
```

```
> (OR2 = (tbl[1,2]*tbl[2,1])/(tbl[2,2]*tbl[1,1]))
[1] 16.5966
> #  (OR2 = 1/OR1)
>
> # Confidence intervals using riskscoreci() from PropCIs package
>
> ### install.packages(package=PropCIs)
> library(package=PropCIs)
> # Putting vax in numerator (row 2 of tbl)
> orscoreci(x1=tbl[2,2], n1=sum(tbl[2,1:2]),
+           x2=tbl[1,2], n2=sum(tbl[1,1:2]), conf.level=.95)
data:

95 percent confidence interval:
 0.04743304 0.07653863

> # Putting unvax in numerator (row 1 of tbl)
> orscoreci(x1=tbl[1,2], n1=sum(tbl[1,1:2]),
+             x2=tbl[2,2], n2=sum(tbl[2,1:2]), conf.level=.95)
data:

95 percent confidence interval:
 13.06530 21.08235
```

Because the probabilities of "success" (hospitalization) are so low, we find that $\widehat{OR} \approx \widehat{RR}$ in each case. The odds of hospitalization are 0.060 times as high with vaccination as without, and the reverse of this is that the odds of hospitalization are 16.6 times as high without vaccination as with. The 95% CIs are (0.047, 0.077) for OR_1 and (13.1, 21.1) for OR_2. Again, we see that the possibility of equal probabilities, $OR = 1$ is eliminated.

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5 What to learn from this

1. Relative risks and odds ratios are two popular measures of association between binary RVs

2. RR is directly interpreted as a ratio of probabilities, which is useful.

   (a) We prefer this measure

3. OR is interpreted as ratio of *odds* which are related to probabilities, but not exactly the same

   (a) But this measure may provide more accurate inferences when the four table counts are not all fairly large (more than 10 or so?)

4. The two measures are very similar when the “success” they are based on is relatively rare.

Table 2: Salk vaccine clinical trial results; see the book for source details.

	Polio	Polio free	Total
Vaccine	57	200,688	200,745
Placebo	142	201,087	201,229
Total	199	401,775	401,974

6 Exercises

Use R for all calculations, unless otherwise specified.

1. One of the most famous and largest clinical trials ever performed was in 1954. Over 1.8 million children participated in the clinical trial to determine the effectiveness of the polio vaccine developed by Jonas Salk. While the actual design of the trial sparked [ethical] debate, we forgo this discussion and focus on the *data* obtained from the randomized, placebo-controlled portion of the trial. The data, given in Table 2, show that 57 out of the 200,745 children in the vaccine group developed polio during the study period, as opposed to 142 out of the 201,229 children in the placebo group. The question of interest for the clinical trial was "Does the vaccine help to prevent polio?"[1]

   (a) Use relative risk to estimate how much higher the probability of polio is in children who are not vaccinated, compared to those with vaccine. Also find a confidence interval for this. **Report the R code and output, and write a sentence interpreting the results.**

   (b) Repeat this, but arrange the relative risk as the reduction in probability of polio that is caused by the vaccine. **Report the R code and output, and write a sentence interpreting the results.**

   (c) Find a 95% confidence interval for the population RR in (b). **Report the code and output, and interpret the results, especially addressing whether there is evidence that the vaccine is effective in reducing the chance that a child contracts polio.**

   (d) I will not ask you to compute the ORs for this problem, but if I did, would you expect them to be similar to the RRs? **Explain in 1 sentence why or why not?**

[1] Description stolen straight from Bilder and Loughin (2014)