

On February 25, 2003, the corporation VaxGen released the results of the first large-scale human trial of a vaccine designed to prevent HIV infection, AIDSVAX.¹ The results were controversial, as the company reported that while the vaccine had no effect on the study population as a whole, the vaccine appeared effective in stopping the spread of the HIV virus among some subgroups, including Blacks.

Yet, the AIDS Vaccine Advocacy Coalition and others say it is too soon to draw any conclusions about the effects of AIDSVAX among subgroups.² Use the information and your responses to the questions below to address this controversy.

Your task is to explain to your boss, who read about this in the newspaper, what this is all about. Why does VaxGen make the claim it does? Why does the AIDS Advocacy suggest caution? What could one do to improve the study to make the results more certain?

Study Design: Volunteers were randomly assigned to either receive the vaccine or a placebo. Neither the volunteers nor those administering the shots knew who got what. In all, 5009 people from high-risk populations participated in the study. The majority of study participants came from the U.S., with others coming from Canada, Puerto Rico, and the Netherlands. They were followed over the three years of the study. Here's some of what VaxGen reported:

	Placebo (Infections/Total)	Vaccine (Infections/Total)
All Volunteers	98/1679 (5.8%)	191/3330 (5.7%)
White and Hispanic	81/1508 (5.4%)	179/3003 (6.0%)
Black	9/111 (8.1%)	4/203 (2.0%)

As you answer the following questions, be sure to formally set up your hypotheses and clearly note the steps you take and the assumptions you make. After you've finished your analysis, summarize them in non-technical language (number 7). For your analysis, use $\alpha = .05$ or 95% confidence intervals.

1. Is the population in this study the same as all high-risk populations? One recent study of a random selection of those at high-risk for HIV infection found the HIV infection rate to be 17.4 percent over three years. Perform a hypothesis test to see if those in the placebo group are the same or different population than that high-risk group. State your assumptions. What explanation do you have for your finding?

$$H_0: p = .174 \quad H_a: p \neq .174$$

Decision rule: $|z| > z_{\alpha/2}$ then reject the null hypothesis

$$\alpha = .05, \quad z_{\alpha/2} = 1.96$$

¹ "VaxGen Announces Initial Results of its Phase II AIDS Vaccine Trial," (Feb 24, 2003) <http://www.vaxgen.com/pressroom/index.html> (Accessed March 15, 2003).

² Brown, David and Rick Weiss. "AIDS vaccine fails test; effect on blacks largely seen as fluke," *Seattle Times* Feb 25, 2003. AIDS Vaccine Advocacy Coalition (March 11, 2003) *Understanding the Results of the AIDSVAX Trial*. <http://www.avac.org/pdf/UnderstandingAIDSVAX.pdf> (Accessed March 15, 2003)

$$z = \frac{\hat{p} - p_0}{\sqrt{\frac{p_0 q_0}{n}}} = \frac{.058 - .174}{\sqrt{(.174)(.826)/1679}} = \frac{-.116}{.009} = -12.54$$

Since $|-12.54|$ is greater than 1.96, we can reject the null hypothesis and say that the true proportion of the population that is HIV positive is not .174—it is likely that the placebo group is not the same high risk group as those in a recent study. It may be that the placebo group, thinking they were getting the vaccine actually reduced the amount of risky behavior and thus lowered their rate of HIV infection. It could also be that those who volunteered for the study were different in some way than the general population of those at risk for HIV. The assumption one must make is that the distribution of the sample proportion follows the normal distribution.

2. Can you confirm VaxGen's report that the vaccine is not effective for the entire population? Perform a hypothesis test comparing results for all volunteers in the placebo and vaccine groups.

Could have done a one-sided or a two-sided test:

$$H_0: p_p - p_v \leq 0 \quad H_a: p_p - p_v > 0$$

$$H_0: p_p - p_v = 0 \quad H_a: p_p - p_v \neq 0$$

$$p_p = .058 \quad p_v = .057 \quad \hat{p} = .0576$$

$$p_p = .058 \quad p_v = .057 \quad \hat{p} = .0576$$

Decision rule: 1-sided test

Decision rule: 2-sided test

$$|z| > z_\alpha$$

$$|z| > z_{\alpha/2}$$

$$\alpha = .05$$

$$\alpha = .05$$

$$z_\alpha = 1.645$$

$$z_\alpha = 1.96$$

$$z = \frac{(\hat{p}_p - \hat{p}_v) - 0}{\sqrt{\hat{p}(1 - \hat{p})\left(\frac{1}{n_p} + \frac{1}{n_v}\right)}} = \frac{(.058 - .057) - 0}{\sqrt{.0576(1 - .0576)\left(\frac{1}{1679} + \frac{1}{3330}\right)}} = \frac{.001}{.007} = .1428$$

We cannot reject the null hypothesis (using either a one-sided or a two-sided test). The placebo and vaccine groups are likely the same, as we do not have enough evidence to say they are different. We can confirm VaxGen's results.

3. Can you confirm VaxGen's report that the vaccine was effective among blacks? Perform a hypothesis test comparing results for black volunteers in the placebo and vaccine groups. What assumption do you need to make to perform this hypothesis test? Is this a valid assumption?

The major assumption we need to make is that the difference in the sampling proportions follows the normal distribution. BUT, that is likely untrue, as np for the vaccine group is only 4, not 5.

Could have done a one-sided or a two-sided test:

$$H_0: p_p - p_v \leq 0 \quad H_a: p_p - p_v > 0$$

$$H_0: p_p - p_v = 0 \quad H_a: p_p - p_v \neq 0$$

$$p_p = .081 \quad p_v = .02 \quad \hat{p} = .04$$

$$p_p = .081 \quad p_v = .02 \quad \hat{p} = .04$$

Decision rule: 1-sided test

Decision rule: 2-sided test

$$|z| > z_\alpha$$

$$|z| > z_{\alpha/2}$$

$$\alpha = .05$$

$$\alpha = .05$$

$$z_\alpha = 1.645$$

$$z_\alpha = 1.96$$

Rejection region on the right (the logic being that if the placebo rate is larger than the vaccine group, then the vaccine is effective). One could certainly have formulated this the other way as well.

$$z = \frac{(\hat{p}_p - \hat{p}_v) - 0}{\sqrt{\hat{p}(1-\hat{p})\left(\frac{1}{n_p} + \frac{1}{n_v}\right)}} = \frac{(.081 - .02) - 0}{\sqrt{.04(1-.04)\left(\frac{1}{111} + \frac{1}{203}\right)}} = \frac{.061}{0.023517} = 2.59$$

We can reject the null hypothesis (using either a one-sided or a two-sided test) at a .05 level of significance. We would see this large a difference in the rates of infection between the placebo and the vaccine group less than 5% of the time if the vaccine were not effective. We can confirm VaxGen's results.

4. How strong is the evidence in part 3?

If we assume the sampling distribution for the difference in the proportions follows the normal distribution, the evidence for the difference is very strong—we have an extremely low

probability of seeing this large a difference if the difference were not real. For a one-tailed test, the p-value is .005. For a two-tailed test, the p-value is .009.

But, it is possible that the assumption was inappropriate.

- Construct confidence intervals around the rate of infection among blacks in the placebo group, among blacks in the vaccine group, and for the difference.

All intervals are 95% confidence intervals

Blacks in the Placebo Group	$\hat{p} \pm z_{\alpha/2} \sqrt{\frac{\hat{p}\hat{q}}{n}} = .081 \pm 1.96 \sqrt{\frac{(.081)(.919)}{111}} = .081 \pm .05$ $P(.03 < p_p < .13) = .95$
Blacks in the Vaccine Group	$\hat{p} \pm z_{\alpha/2} \sqrt{\frac{\hat{p}\hat{q}}{n}} = .02 \pm 1.96 \sqrt{\frac{(.02)(.98)}{203}} = .02 \pm .01$ $P(.01 < p_v < .03) = .95$
Difference for Blacks in Placebo and Vaccine Groups (in my CIs, P1=placebo, P2=vaccine)	$(\hat{p}_1 - \hat{p}_2) \pm z_{\alpha/2} \sqrt{\frac{\hat{p}_1(1-\hat{p}_1)}{n_1} + \frac{\hat{p}_2(1-\hat{p}_2)}{n_2}}$ $= (.081 - .02) \pm 1.96 \sqrt{\frac{(.081)(1-.081)}{111} + \frac{.02(1-.02)}{203}}$ $= .061 \pm 0.05$ $P(.01 < p_1 - p_2 < .11) = .95$

So, 95 times out of 100, the true rate of infection among Blacks in the placebo group will be between 3% and 13%, among Blacks in the Vaccine group, it will be between 1% and 3%. We are also 95% confident that blacks in the placebo group had between a 1 percentage point and 11 percentage point higher rate of infection than blacks in the vaccine group.

6. How large a sample of each group would you need to detect a significant difference if you want to come within .02 of the difference between the groups? (To figure this out, you'll need an estimate of the variance of the difference in the means, estimated using this equation: $p_1q_1 + p_2q_2$. The result with this substitution provides the number needed in each group.)

$$n_1 = n_2 = \frac{z_{\alpha/2}^2 (p_1q_1 + p_2q_2)}{B^2}$$
$$= \frac{1.96^2 ((.081)(1-.081) + (.02)(1-.02))}{.02^2} = 903$$

So, we would need 903 study participants in each group in order to estimate the difference between those groups to plus or minus .02 with 95% confidence. (see page 420 for more on this)

7. Summarize and interpret your results for your boss, a non-technical policy maker who has an interest in learning about the dynamics of this landmark AIDS vaccine study. Make sure to explain the controversy, whether you can confirm the study's findings, and the implications of the study's sample sizes. End with an assessment of whether, based upon your results, you would trust the study's findings concerning Blacks. (25 points)