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Controlled and Natural Experiments

Some number of years ago, your blogger participated in a regular (a couple of times per month) poker game with some folks from the National Institute of Health (NIH). On a really good (bad) day, a player could win (lose) forty or fifty dollars. Most often it was far less than that.

One day, YB got into an animated discussion with an NIH statistician in which the statistician insisted that one could get no useful information other than from a controlled "double-blind" also known as "double-masked" study. In the vernacular, a double-blind test occurs when neither the researcher administering the treatment nor the treatment recipient knows whether he/she is getting the treatment. Along with randomization, where both the placebo and control groups are theoretically the same (age, gender, socioeconomic status) this helps to prevent confounding and bias thus creating the gold standard of a randomized controlled trial or RCT. The randomization prevents confounding and the double-blinding prevents bias. This is the study design that researchers have sought to use in trials to develop the various COVID-19 vaccines. YB knows a few people who participated in such trials. One has had four COVID-19 shots, in part because he was subsequently informed that his first dose in the trial was of an inactive "placebo" test.

This is a health economics blog, and economists seldom have the luxury of RCTs. When economists look at demand for housing, for example, prices, incomes, and interest rates all vary, as well as housing market conditions across the country. They call these "natural experiments." Depending on the question at hand, empirical economists must employ complex, sometimes multiple equation models, that recognize that various processes are occurring at the same time.

In the early days of 2021, when the COVID-19 vaccinations were first available, hopes soared that the vaccines would deliver a "knockout" punch to the coronavirus. People would get the vaccines and the virus would end! As we finish the summer, and as COVID-19 deaths edge over the 1,000 per day level again, it is helpful to examine what the double-blind models have missed, and what will have to be examined with messier, "unblinded" methods.

It has become clear that to understand the aggregate impact of COVID-19 on society, researchers must "model" the following behaviors:

1. Vaccine hesitancy – What are the characteristics and numbers of how many people reject the vaccine? Is vaccine hesitancy more common among certain social groups, related to race/ethnicity, age, or geographic location?
2. Infectiousness of those who are vaccine hesitant – See item 1.

3. Behaviors of those who are vaccine hesitant – Who, and how many people do those who are vaccine hesitant interact with? Were they masking? Were they "social distancing?" What kinds of groups are they in? Were they outside or inside?
4. Behaviors of those who have been vaccinated – See item 3.
5. Whether vaccination leads to "riskier" behaviors that have led to "breakthrough" cases of COVID-19?
6. Community transmission of the COVID-19 virus, given items 1 – 5.

The types of models to be used must account for the fact that some people "select themselves" into vaccine hesitancy – this is not random. Different groups interact differently. This, too, is not random. This induces selection bias and counteracts the idea of randomizing groups to avoid confounding. We know who is indeed vaccinated, which eliminates the double-blind aspect. Community transmission and spread takes all of these behaviors, and distills them in a decidedly nonrandom way. The percentage and absolute number of COVID-19 cases is a function of the vaccine efficacy, and ALL SIX of the behaviors listed above.

So, a double-blind RCT is the gold standard. The real world is a messier place than the laboratory, requiring complicated models to explain the far messier natural experiments that are going on.

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* Your blogger is grateful to Sara Goodman MPH for important clarifications in the characterization of double-blind experiments.