**Unit: Theory of Vaccination**

Sahotra Sarkar
University of Texas

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1. Throughout we will have Covid-19 at the back of our minds. This is *not* reflected in the recorded lectures which are from 2019.
2. We will begin with how vaccination works in the case of the individual. It requires some understanding of the immune system.
3. In vaccination, some substance is introduced into the body in some way, typically orally or through injection.
   - This substance, the *vaccine*, induces an immune response from the body.
   - This response includes the proliferation of B cells (which are white blood cells/lymphocytes) that produce a specific *antibody*.
   - Thus, the vaccine serves as an *antigen*.
   - The vaccine is so chosen that it mimics the shape and size of the targeted infectious agent (pathogen).
   - The vaccine is so designed that it cannot cause an illness.
     - Typically the vaccine consists of or uses part of the pathogen.
     - For instance, if only part of the pathogen is used, it cannot reproduce.
     - For instance, if a live pathogen is used, then it can be so attenuated as to not cause disease symptoms.
     - This is one of the places where things can go wrong, for instance, in the case of pertussis for which live cells were used in vaccines at one time before being replaced by **a**cellular **p**ertussis pathogen extracts (the "AP" in TDAP).
   - Once vaccinated, the body has *immune memory* of exposure to the vaccine. This means that, should the body encounter that vaccine again, it has B cells in place to mount and immediate and strong response.
   - It also means that, should the body encounter the targeted pathogen, it has B cells in place to mount an immediate and strong response.
   - The body thus has *acquired immunity* to the pathogen in the same way it would have had it been invaded by the pathogen itself.
4. This, pretty much, is the extent of our theoretical understanding of how vaccines work (though, of course, there are many details that have been worked out).
   - There is much that we do not theoretically understand.
   - This lack of understanding is about the relevant immune mechanisms themselves, and not just about vaccination.
   - For instance, we know that different vaccines confer immunity for different periods of time.
     - We know this from empirical data, not from any theoretical understanding.
     - For each vaccine, we find out from field trials and other data how long immunity through vaccination lasts.
     - This lack of theoretical understanding is why, in the case of Covid-19, there is *uncertainty about whether even infection confers immunity* (to re-infection).

5. We should acknowledge that there have been many safety problems with vaccines throughout their history.
   - This partly accounts for the traditional anti-vaccination movement.
   - It does not explain the current anti-vaccination movement centered from Austin and the fraudulent claims by defrocked "doctor" Andrew Wakefield asserting a link between the MMR [measles-mumps-rubella] vaccine and autism.
6. Let us turn briefly to the design of vaccines against Covid-!9.
   - The most important attempts are those that attempt to do this de novo by finding molecules that mimic the surface shape of the Covid-19 coronavirus particle.
   - However, it is equally important (as in the case of drugs) to see if existing alternatives have some value.
     - For instance, existing vaccines against other coronaviruses and similar viruses may have some specificity against Covid-19.
     - This can be judged at a preliminary level to see if there is a correlation between those who have had this vaccine and those who have been exposed to Covid-19 but not succumbed to it.
     - If so, the next step is to see if we have a credible molecular inerpretation of these results.
     - Then the candidate vaccine can be tried on animal models.
     - Note that, by and large, we will not need new human safety studies because these viruses are already being used in humans.
     - Some positive statistical correlations have been reported for the BCG vaccine (against tuberculosis).
     - Even more promising statistical correlations have been reported for the MMR vaccine.
       * Molecular inspection shows that what is likely to be involved is the rubella component,
       * There is suggestive ancillary data that suggest that this possibility is worth exploring more seriously.
         · Individuals born before around 1962 are likely not to have had this vaccine because it was not available.
         · They are also exempt from it today because they are very likely to have been exposed to measles (and to have had the disease in childhood) and only slightly less likely to have been exposed to mumps.
         · However, rubella was much rarer.
         · We see the highest susceptibility to Covid-19 in exactly this group.
       * *These observations must not be over-interpreted.* But it is a research possibility worth pursuing.
7. Let us turn to the population level.
   - The crucial question is herd immunity, what it means, why it matters, and what its limitations are.
   - There are also serious ethical issues connected with mandatory vaccination.
     - There is the ever-present potential conflict between social good and individual liberty.
     - On the other side, thanks to what herd immunity can accomplish, there are potential free-rider problems.
8. Theory of herd immunity.
   - The basic idea is the following: if a sufficient proportion of a population is immune to a pathogen, then it cannot spread even if introduced because most of the contacts of the infected person would not be susceptible to the infection and would not spread the disease.

- It is time to quantify this argument:
  (a) Let one individual $X$ of a population $P$ be infected.
  (b) Let the proportion of $P$ that is immune to the infection be $v$. (Here $v$ stands for "vaccinated" because we are in the context of vaccination. But the argument is more general.)
  (c) Let $s$ be the proportion of $P$ that is susceptible. Then $s = 1 - v$.
  (d) Let $R_0$ be the number of individuals of $P$ with whom $X$ comes into *infective contact*. Here, "infective" means that the contact is of such a form that disease can be transmitted. For instance, for HIV/AIDS this requires blood-to-blood contanct and $R_0$ is very low. For Covid-19, all that is required is one person to have breathed in virus particles breathed out by an infected person. So, $R_0$ can be high. $R_0$ is known as the *basic reproduction number*. Assuming *complete mixing* (that any two individuals of the population are equally likely to come into infective contact), the expected number (that is the average) of individuals infected by $X$ is $sR_0 = (1 - v)R_0$.
  (e) We must consider three possibilities:

     | | |
     |---|---|
     | $sR_0 = (1 - v)R_0 < 1$ : | In this case the infection cannot spread. It will get smaller and smaller. |
     | $sR_0 = (1 - v)R_0 = 1$ : | In this case the infection will persist but cannot spread on the average but can fluctuate. |
     | $sR_0 = (1 - v)R_0 > 1$ : | In this case the infection can spread. |

  (f) This means that the case of $sR_0 = (1 - v)R_0 = 1$ acts as a threshold and we will denote the relevant variables as $S_c$ and $v_c$ where $c$ is for "critical" indicating the existence of a threshold.
  (g) Let us work out this case in some detail:

$$
\begin{aligned}
s_c R_0 &= 1 \\
1 - v_c R_0 &= 1 \\
R_0 - v_c R_0 &= 1 \\
v_c R_0 &= R_0 - 1 \\
v_c &= \frac{R_0 - 1}{R_0} \\
v_c &= 1 - \frac{1}{R_0}
\end{aligned}
$$

  (h) This equation gives the crucial insight about what the vaccination rate must be in order for an infection not to spread.
  (i) A little algebra shows that $v_c$ has yet another important interpretation.
     - Let $e$ be the effectiveness of a vaccine. Then, with $0 < e < 1$, if $n$ individuals are vaccinate, the number of those who acquire immunity is $en$.
     - If $e > v_c$, the vaccine cannot prevent the spread of the disease.
     - Thus, we should be wary of claims such as the one made by Fauci that he would be happy with a vaccine that is 70 % effective. Such a vaccine could not control the spread of Covid-19 in the U.S. unless, of course, (as is very likely) a fairly large proportion of individuals are also acquiring immunity through infection itself.
  (j) For Covid-19 $R_0$ is believed to lie between 2 and 4. Contras that with measles where it is supposed to lie between 12 and 18. So, why didn't we end up with lockdowns, quarantines, *etc.*, last year when measles epidemics had spread around the world.
     - This answer and **I do not know how to emphasize it more**: even though measles is far more infective than Covid-19 *it could not produce a pandemic of current proportions because almost all people in rich countries and most people in most other countries had been vaccinated against measles using MMR.* Moreover, MMR is a very effective vaccine with $e \geq 0.9$; otherwise measles would be out of control.

(k) The formula also shows the importance of social distancing.

(l) Returning to our Covid-19 calculations, the required vaccination rate $v_c$ lies between 50 % and 75 %.

- This is not intractably high. This is a rate easily achievable through a concerted mandatory vaccination campaign if there is a political will for it.
- Moreover, if a significant number of individuals may be acquiring immunity through infection. Suppose that the fraction is 10 % which may be an underestimate for localities that have seen a spike of cases. Then the required vaccination rate become between 40 % and 65 %.
- All this explains the urgency of vaccine design.
- The real problem is the anti-vaccination movement. Fauci has correctly noted that it may be the greatest obstacle we face in achieving herd immunity.

(m) Finally, note that many factors make $v_c$ an upper limit for the required vaccination rate. There are many factors that lower it.

- The assumption in the calculation that requires most scrutiny is complete mixing. (This is an issue that is important in many other ecological and evolutionary contexts. As a result it is well-studied.)
- Populations have spatial structure. Those who are far from each other are less likely to be involved in infective contact than those closer together. (This is the principle behind social distancing.)
- Populations have age structure. Not having the mobile young in contact with more vulnerable elderly sessile family members is a good idea.

9. Finally, let us turn to the most important ethical problems of vaccination.

10. First, there is the question of he ethics of vaccination itself. Should we vaccinate someone?

(a) Within this context, because of vaccine safety issues, we can ask whether we should vaccinate anyone, particularly, a young child.

- Vaccines have a long history of lack of safety—Mnookin (2011) provides a relatively unbiased history.
- Concerted attempts have been made to make vaccines safer but there is always a small risk.
- A (tiny) fraction of those vaccinated by *any* vaccine get seriously ill and a very small number die.
- What risk we are willing to accept is a normative question (of social values).
- Unfortunately, answers to this question have become enshrined in policy without explicit informed social discussion. *This is what must be changed.* Self-styled experts should not be allowed to hide behind their lab. coats.

(b) Then there is the question of mandatory vaccination.

- We will be very short here because this is the topic of the next lecture.
- Note that this is yet another instance of the standard conflict between the public good and individual liberties. (I keep on emphasizing this.) Nevertheless, there are two specific points that should be borne in mind.
  - The anti-vaccination movement invariably raises the issue of parental rights which has a lot of emotive appeal in the U.S. though not everywhere else. However, do parents have the right to put their children at risk of disease? Or is this child abuse? Note that child abuse is a criminal issue. But where do we stop? Is religious indoctrination child abuse?
  - Vaccination is intensely personal in the sense that a potential (highly unlikely) dangerous substance is being injected into your body. Shouldn't you have every right to refuse it? (And recall how Oliver Wendell Homes used the analogy to vaccination to allow the involuntary sterilization of Carrie Bell.)

- What I wish to emphasize is that the concerns of the anti-vaccination movement should be addressed and not dismissed out of hand.

11. Second, there is the free-rider problem (which also occurs in many other contexts).

    - Vaccination has a cost in terms of the cost of the medication (which, at least in the U.S. is typically not borne by the vaccinated individual) as well as the discomfort and psychological cost of worrying about the risk. As a result of a lot of people paying this cost, a population achieves herd immunity. Now consider an individual who is capable of being vaccinated (that is, not too young or too old or immune-compromised) but refuses to do so. This individual reaps the benefit of herd immunity without paying the cost, Isn't this unethical?
    - Suppose the individual says that it is fine with the person to take the risk of individually suffering from the disease. Does this resolve all the ethical issues.
    - Suppose we have enough free riders that herd immunity is lost. This puts at risk those who should be medically exempt from vaccination, the very young, the very old, those who are immune-compromised due to disease or some other reason, and so on. What ethical problem does this add to vaccine refusa beyond free-riding?

**References**:


- Mnookin, S. 2011. The Panic Virus: A True Story of Medicine, Science, and Fear. New York: Simon and Schuster.