Educational corner: Testing for antibodies, Bayes formula and the difficult conditional probabilities

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In each issue we present some short educational text about a subject in mathematical biology. If you think some subject should be treated in the next issue, please let us know. Enjoy!

An important unknown in the current corona-crisis is the so-called *dark figure*, the proportion of the population that have been infected with SARS-CoV-2, the virus that causes COVID-19, and therefore is assumed immune to the disease (which is another important unknown! We do not yet know whether the presence of antibodies means that you are immune to the coronavirus in the future; or if you are immune, how long it will last). Why is that so important? From a predictive point of view, this number is essential because predictions of future cases heavily depend on it - the larger the proportion of immune and not infectious in a population, the less spread of the disease. But also from a personal point of view, we would like to know if we are immune, and therefore do not risk neither to get sick, nor to infect others. However, it turns out that even if we can conduct reliable population studies that can reveal the dark figure, it is much more difficult to estimate exactly *who* are the individuals that are immune. This is due to a tricky and counterintuitive effect when small probabilities are in play.

A COVID-19 antibody test, also known as a serology test, is a blood test that can detect if a person has antibodies to SARS-CoV-2, and therefore has had a COVID-19 infection. Many antibody tests are currently under development, and by now many good tests are available, where "good" means that they have a high *sensitivity* and a high *specificity*. Sensitivity is the probability of the test to correctly identify a person with antibodies, also known as the *true positive rate*. A highly sensitive test will identify most people who truly have antibodies, and only a small proportion of the people with antibodies will be missed by the test (*false negatives*). Specificity is the probability of the test to correctly identify a person without antibodies. This is known as the *true negative rate*. A highly specific test will identify most people who truly do not have antibodies, and only a small proportion of the people without antibodies will be identified as having antibodies by the test (*false positives*). By now, many tests are available with a sensitivity of nearly 100% and also a high specificity of around 95-99% [1]. With so high probabilities, we would indeed believe that we can trust the result of the test! However, let's see why that is not so.

The *positive predictive value* is the probability that people who have a positive test result truly have antibodies. This is *not* the same as the sensitivity, and this is why this is so tricky. To see this, let's define two events: A is the event that a person has antibodies, B is the event that a person has a positive test result. Then we have the following *conditional probabilities*

$$\text{Sensitivity } = P(B|A)$$

and

$$\text{Positive predictive value } = P(A|B)$$

where $P(A|B)$ denotes the probability that A is true *conditional* on B being true, and likewise for $P(B|A)$. These are not the same! It is the positive predictive value, we are interested in, when we get tested and want to know what the probability is that we are immune, given the test was positive. The positive predictive value depends on the *prevalence*, the proportion of the

population that have antibodies (the dark figure) at the time of the test, that is, the *marginal* probability,

$$\text{Prevalence } = P(A).$$

Bayes' theorem states that

$$P(A|B) = \frac{P(B|A)P(A)}{P(B)}$$

where we assume $P(B) > 0$. Thus, we see that these two conditional probabilities are only the same if $P(A) = P(B)$. This is only the case if the sensitivity and the specificity of the test are 100%, which is rarely (if ever!) the case for any test. Moreover, their ratio becomes quickly very small if the prevalence is low, as is the case for SARS-CoV-2 antibodies, at least in most places at this stage of the endemic, so the two conditional probabilities can be very different. Let's do the calculations. The probability $P(B)$ can be found by the law of total probabilities,

$$
\begin{aligned}
P(B) &= P(B|A)P(A) + P(B|\text{not}A)P(\text{not}A) \\
&= \text{sensitivity } \times \text{prevalence} + \\
&\quad (1 - \text{specificity }) \times (1 - \text{prevalence}).
\end{aligned}
$$

Thus, the lower the prevalence, the lower the predictive value! This means that COVID-19 antibody tests, even with high sensitivity and specificity, used in areas with low prevalence will have a lower positive predictive value than in an area with higher prevalence. The prevalence is probably strongly varying from area to area, but in many places, an estimate of 2-5% is likely not far from the truth at the time of writing. Let's assume a test with sensitivity of 100% and specificity of 98%, used in an area with prevalence of 2%. Then the positive predictive value is

$$P(A|B) = \frac{0.02}{0.02 + (1 - 0.98)(1 - 0.02)} = 0.5.$$

Even with such a good test, the chance of having had COVID-19 is only fifty-fifty if you test positive for antibodies!

The reason is that there are two unlikely events in play: the probability that you are immune (a small probability, given by the prevalence), and therefore will be tested positive (with a large probability, in the example above with probability one) – or the probability that you will be tested positive, even if you do not have antibodies (a small probability), but many people without antibodies will be tested (because the prevalence is small), and thus, the number of false positive will be large.

Why this is so counterintuitive is beautifully explained in the highly recommendable book by Nobel prize winner Daniel Kahneman [2], for example in chapter 14, where it is shown how we psychologically tend to forget or ignore base rates (the prevalence) in the light of further information (the outcome of the test).

A low positive predictive value will lead to more individuals with a false positive result, which is dangerous, since a positive test result most likely will make us more relaxed about maintaining cautious behaviours to not become infected or infect others. In this particular example, we can be sure we do not have antibodies if we get a negative result since the sensitivity is 100%, so there are no false negatives.

Note than even if it is difficult to identify the specific individuals that have antibodies, we can use the tests to obtain good estimates of the prevalence if we test many, since we can correct for the expected number of false positives and false negatives. Thus, reasonable population estimates are available, even if personal estimates are not.

References

[1] FDA U.S. Food & Drug Administration. EUA Authorized Serology Test Performance. https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/eua-authorized-serology-test-performance. Retrieved on September 9, 2020.

[2] D. Kahneman. (2020). Thinking, Fast and Slow. *Penguin Books*. 2011