**COVID Update 139**. Home antigen tests: how to use them for safer holiday gatherings; how to interpret antigen test results

If you are planning to use home antigen testing for the SARS-2 virus to increase the safety of holiday gatherings, you are not alone. A recent survey indicates that a majority of people are planning to follow safety precautions, including home testing of guests. See: "Survey finds most Americans will still use COVID precautions this holiday season" OSU Wexner Medical Center
http://osuwmc.multimedia-newsroom.com/index.php/2021/02/08/survey-most-americans-will-continue-health-precautions-after-covid-19/

In this Update, I will talk about the testing science in some recent papers, and use their data to make calculations to show why home antigen tests can be very effective for screening yourself and guests just before holiday gatherings. No test is perfect or foolproof, of course. But if you are actively shedding live virus, and are therefore more likely to be able to transmit it to others, the probability turns out to be very high that a home antigen test will catch that. I'll get into the science and the numbers, but that's the bottom line.

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**1. How are public health experts managing holiday gatherings?**
An article in the NYT has an informative Q&A with three top experts: Prof: Linsey Marr (aerosol scientist who studies airborne transmission of viruses); Dr. Juliette Morrison (virologist at U. Cal, Riverside); and Dr. Jennifer Nuzzo (epidemiologist at Johns Hopkins School of PH). They responded to questions submitted from NYT readers, and offered suggestions for steps to manage risk at holiday gatherings. Some of their suggestions:

- Take into account the prevalence of COVID in both the locality where the gathering is held, and in the (distant) communities from which family members and guests will be arriving.
- Consider gathering only with fully vaxed family members (kid exception) and guests.

- Have guests take rapid antigen tests no more than 1 day ahead of a gathering, and preferably on the day.
- Improve indoor ventilation (open some windows, use room HEPA air filtering systems).
- Separate (vaxed) adults from (unvaxed) kids during sit-down dinners, when masks are off.

Full article: “Can Covid Winter Be Merry and Bright? We Asked the Experts.” NYT, 17 Nov 2021.
https://www.nytimes.com/2021/11/17/opinion/covid-thanksgiving-holiday-risk.html

A recent statnews questionnaire asked public health experts, epidemiologists, immunologists, and virologists about their comfort level with a range of activities, including holiday gatherings. Some of these experts were interviewed by Helen Branswell to discuss the precautions they would take. See: “What would the public health experts do? STAT asked 28 about their holiday plans amid Covid-19.” statnews, 10 Nov 2021.
https://www.statnews.com/2021/11/10/covid19-pandemic-thanksgiving-christmas-movies-gym/?utm_source=STAT+Newsletters&utm_campaign=3c3a69e0f6-MR_COPY_01&utm_medium=email&utm_term=0_8cab1d7961-3c3a69e0f6-152214218

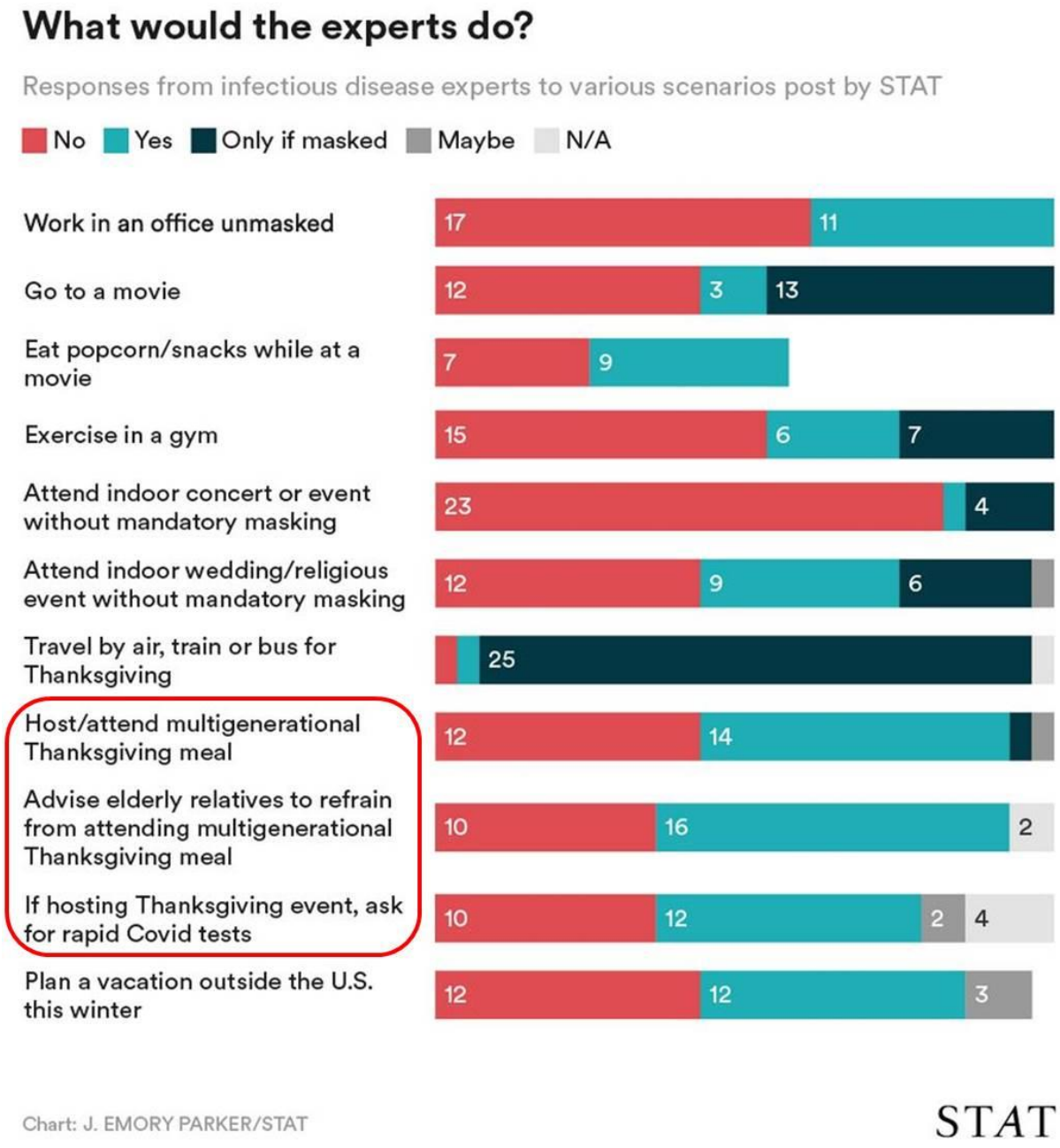
Most of the questions required a “Yes” or “No” answer; many also could be answered “Masked”, shorthand for “Yes, I’d do this, but I would wear a mask while doing it.” Some questions elicited a “Maybe” or two. In many cases, the answers came with caveats. Here is a graphical summary of the responses from the article.

Half of the 24 experts who responded to the rapid COVID testing question indicated that if hosting, they would ask guests to take a rapid test on the day. Another 2 said maybe they would.

Dr. Michael Mina, a professor of epidemiology at Harvard’s T.H. Chan School of Public Health was not among those surveyed. But he has said that to ensure greater safety at his holiday gatherings, he will ask all attendees, even if vaccinated, to take a rapid home antigen test, starting with himself. This testing will screen everyone, so that all can be more confident that spending the day together indoors, and especially eating and drinking in close proximity with masks off, will be reasonably safe.

This choice is not surprising, as Dr. Mina has long been an advocate for affordable COVID antigen test kits that produce rapid results for in-home screening. He has a website with lots of good info on that: https://www.rapidtests.org/

Figure 1.




**2. PCR and antigen tests: what they are, and how they work.**
During most of 2020, the only tests available were PCR tests. These early tests used a mucus sample taken with a deep nasopharyngeal swab (described by some as a “brain stab”). Today, these tests can use either a saliva sample swabbed from the mouth, or a swab from the anterior nares, which only has to be inserted ¾ of an inch, and twirled around in each nostril. Antigen tests such as Abbott’s BinaxNOW and Quidel’s QuickVue also use this much less uncomfortable swab method.

A PCR test detects the presence of viral RNA. It is designed to have very high specificity (generally greater than 98%), meaning that it can tell the difference between the genetic sequence for the SARS-2 virus and other viruses, including influenza and more benign coronaviruses that cause common colds. PCR is a shortened abbreviation of the full name of the test: reverse transcription polymerase chain reaction (RT-PCR), or sometimes quantitative RT-PCR (abbreviated RT-qPCR).

RT-PCR tests use a multi-step process. The first step uses reverse transcriptase to convert any RNA fragments in the sample into complementary DNA (cDNA). The second step is an amplification step that uses a polymerase chain reaction to duplicate and amplify the cDNA to make it easier to detect. The PCR amplification is usually repeated 40 times. Each iteration, called a cycle, results in a doubling of the cDNA. So after 40 cycles, there will be 2^40 times as much genetic material (many billions more copies) compared to what was present in the original sample. The main result of a PCR test is qualitative: the amplified viral genetic material is either detected or not. But some labs also report a quantitative result, the cycle threshold value, denoted $C_t$. This is the number of cycles it took to detect with high confidence the presence of SARS-2 viral genetic material. A lower $C_t$ value indicates larger amounts of SARS-2 RNA were present on the swab. Next time I'll cover some recent science that has established a correlation between Ct, and the likely number of virions per unit volume, which is in turn correlated with infectiousness.

In addition to their high specificity, because PCR tests can amplify even minute quantities of viral RNA in a sample, they also have high sensitivity (generally greater than 95%).This means the probability is very high that the test will be Pos if there is SARS-2 RNA in the sample. But there is a downside to the high sensitivity of PCR tests. Depending on the stage of infection, viral RNA found in your mucus might be from live infectious virions; or it might just be part of the viral debris from killed virions; or a combination. This is why people can still get a Pos PCR test result for many days after the infection has been beaten back and they are no longer contagious or transmitting live virus.

Antigen tests are designed to detect nucleocapsid (or N) proteins from the surface capsule of the SARS-Cov-2 virus. The N proteins are different from the spike (or S) proteins we hear so much about, which are also on the outer surface of the viral capsule. Both types of proteins are referred to as antigenic, but these antigen tests are looking specifically for viral N proteins. Unlike PCR tests, antigen tests do not amplify the viral molecules in the sample. They typically use a process known as lateral flow immunoassay (LFIA), the same technology commonly used in home pregnancy tests.

One item from the fine print that hopefully doesn't arise: the N-protein from the original SARS-1 virus (circa 2003, in Hong Kong, Singapore, and China) is either identical or nearly so, to the N-protein from SARS-CoV-2. The detected presence of either will result in a Pos test result for these antigen tests.

The details of how a mucus sample is transferred from the swab to a solution, and how the LFIA test strip receives the sample-bearing solution can vary. One segment of the test strip is impregnated with antibodies that are conjugated to inactive labeling compounds. The antibodies are chosen so that they bind specifically to the N protein antigens of the SARS virus on contact. If this antigen/antibody binding happens, the label attached to the antibody is activated, and produces a visual signal (fluorescence, for example). The test strip is designed to create lateral flow of the sample solution through a field of inactivated conjugated antibodies. Agglutinated complexes of antigen/antibody/label will form and migrate farther along the test strip, to a sample readout point, where they accumulate. The process takes 10-15 minutes (depending on the brand of test), and if a significant amount of antigen was present in the sample, a visible line will appear at the test point on the test strip. The line will be faint or bright, depending on how much viral antigen was present in the sample. Interpreting this line at home is a subjective process. The instructions in the Quidel and Abbott test kits give visual examples as an aid. Abingdon Health has a cool animated movie that shows how the process works, with their particular lateral flow immunoassay technology. This is worth watching if only because of the upbeat background music. See:
https://www.abingdonhealth.com/videos/how-does-a-lateral-flow-immunoassay-work/

Antigen tests generally have very high specificity (greater than 98%), which makes them as good as PCR tests for discriminating between SARS-2 and other viruses. But because there is no amplification of the N proteins, antigen tests will be less sensitive than PCR tests, when it comes to detecting small amounts of virus or viral debris. However, there is now strong evidence that when a person is producing enough virus to be contagious, an antigen test can have sensitivity comparable to a PCR test. This is important news, because it establishes the value of using in-home antigen tests for screening: these tests are particularly good for screening symptomatic people; but they are also able to screen asymptomatic people who may be in the early stages of shedding virus.

Antigen and PCR tests are “biologically orthogonal.” This term of art means that the tests are measuring different types of viral molecules on/in the virus. Therefore, if you get a Pos result from a home antigen test, a follow-up PCR test can be used to confirm the preliminary antigen result, without the possibility that the two results are wrong for the same reason. Mathematically, the tests are said to be independent, because they provide uncorrelated measurements of the presence of virus.

For more info on RT_PCR tests, see:
https://en.wikipedia.org/wiki/Reverse_transcription_polymerase_chain_reaction

PCR tests are one type of a broader category of nucleic acid amplification tests (NAATs). For more details on PCR and alternatives like LAMP, NEAR, and TMA, see:
“Nucleic Acid Amplification Tests (NAATs).” CDC, last updated 16 Jun 2021.
https://www.cdc.gov/coronavirus/2019-ncov/lab/naats.html

For more info on antigen tests and testing strategies, see: “Interim Guidance for Antigen Testing for SARS-CoV-2.” CDC, last updated 9 Sep 2020.
https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antigen-tests-guidelines.html

**3. Test accuracy: sensitivity and specificity for Abbott and Quidel home antigen tests**

Test accuracy is characterized by two parameters, sensitivity and specificity (S&S). A test with low sensitivity will not be capable of detecting all cases of infection, and will therefore have a high rate of false Neg results, so its positive predictive value (explained below) will be lower. A test with low specificity may not be able to discriminate between the SARS-2 virus and other less harmful coronaviruses that are present, so it will sometimes generate false Pos results when SARS-2 is absent, but one of the other viruses is present.

Before the FDA grants emergency use authorization to a test maker for a new COVID test, the maker must submit S&S estimates for the test, as measured with calibration studies done by the test maker or an independent lab. These studies usually involve collecting swabs from 50-200 people who may not yet be diagnosed at time of testing. Subjects are usually not specifically pre-selected because they are thought to have COVID, so each subject is exhibiting symptoms that fall somewhere on a spectrum: everything from no symptoms to one or more symptoms indicative of what is summarized as flu-like illness (cough, sneezing, headache, fever, muscle aches, labored breathing). It is not known in advance whether any of these subjects have COVID, so duplicate swabs are taken. One is used in the antigen test being calibrated, the other is processed by a reference PCR test, and the results are compared to see how well the antigen test tracks the PCR reference test. One consequence of this is that the resulting S&S estimates submitted to the FDA are averaging the accuracy that would be measured if testing only symptomatic people, with the accuracy that would be measured if testing only asymptomatic subjects.

In the table below, I show what those manufacturers’ statistics look like, for three antigen tests, Abbott’s BinaxNOW and Quidel’s QuickVue At-home, and Quidel’s SARS FIA assay on a portable Sofia machine. The two home tests are now commonly available at CVS and Walmart, in the U.S.

S&S estimates are usually expressed as percentages, up to 100%. Because they are statistical estimates from study data, they always come with credible intervals (CIs). Also shown for comparison, are the statistics for two good PCR tests, Roche’s SARS-CoV-2 assay, run on their cobas 6800 machine; and Abbott’s SARS-CoV-2 assay, run on their Alinity m series lab machine.

The nominal false Neg rate for antigen tests like QuickVue and BinaxNOW is significant (15.4% - 16.5%) when compared to most PCR tests (2% - 4%). But these two antigen tests also have low false Pos rates (0.8% - 1.5%), which are as good as most PCR tests.

Table 1. Some antigen and PCR test accuracies from maker's specs.

| Maker | Test name | test type | sensitivity | sensitivity 95% CI | specificity | specificity 95% CI | false Neg rate | false Pos rate |
|---|---|---|---|---|---|---|---|---|
| Abbott | BinaxNOW | antigen, home | 84.6% | (76.8 - 90.6%) | 98.5% | (96.6 - 99.5%) | 15.4% | 1.5% |
| Quidel | QuickVue | antigen, home | 83.5% | (74.9 - 89.6%) | 99.2% | (97.2 - 99.8%) | 16.5% | 0.8% |
| Quidel | SARS Antigen FIA assay on Sofia | antigen, portable clinic | 96.7% | (83.3 - 99.4%) | 100.0% | (97.9 - 100%) | 3.3% | 0.0% |
| Roche | SARS-CoV-2 assay on cobas 6800 | RT-PCR, lab | 96.4% | (87.7 - 99.0%) | 98.0% | (95.6 - 99.1%) | 3.6% | 2.0% |
| Abbott | SARS-CoV-2 assay on Alinity m | RT-PCR, lab | 96.5% | (87.9 - 99.6%) | 100.0% | (92.5 - 100%) | 3.5% | <1% |

Sources:
https://quickvueathome.com/wp-content/uploads/2021/08/EF1500200EN00.pdf
https://www.fda.gov/media/141887/download
https://www.quidel.com/sites/default/files/product/documents/EF1438906EN00.pdf
https://www.molecular.abbott/sal/53-60819R7_Alinity_m_SARS_CoV_2_AMP_KIT_PI_EUA.pdf

**4. Why antigen tests are better than the nominal specs suggest: higher sensitivity during onset and early days of contagious window**

On his rapidtests.org website, Michael Mina notes that there is good scientific evidence that antigen tests make excellent "contagiousness tests." And, "Rapid [antigen] tests can't detect every case, but they're excellent at detecting when you have enough virus to be contagious. Most cases missed by rapid tests happen after people have stopped being contagious, when only deactivated fragments of viral RNA remain."
https://www.rapidtests.org/blog/antigen-tests-as-contagiousness-tests

A number of recent studies have shown very encouraging data about the accuracy of antigen testing. Here is one of the first studies published: Rebecca L. Smith, et al, "Longitudinal assessment of diagnostic test performance over the course of acute SARS-CoV-2 infection." Journal of Infectious Diseases, 21 Sep 2021.
https://academic.oup.com/jid/article/224/6/976/6311835

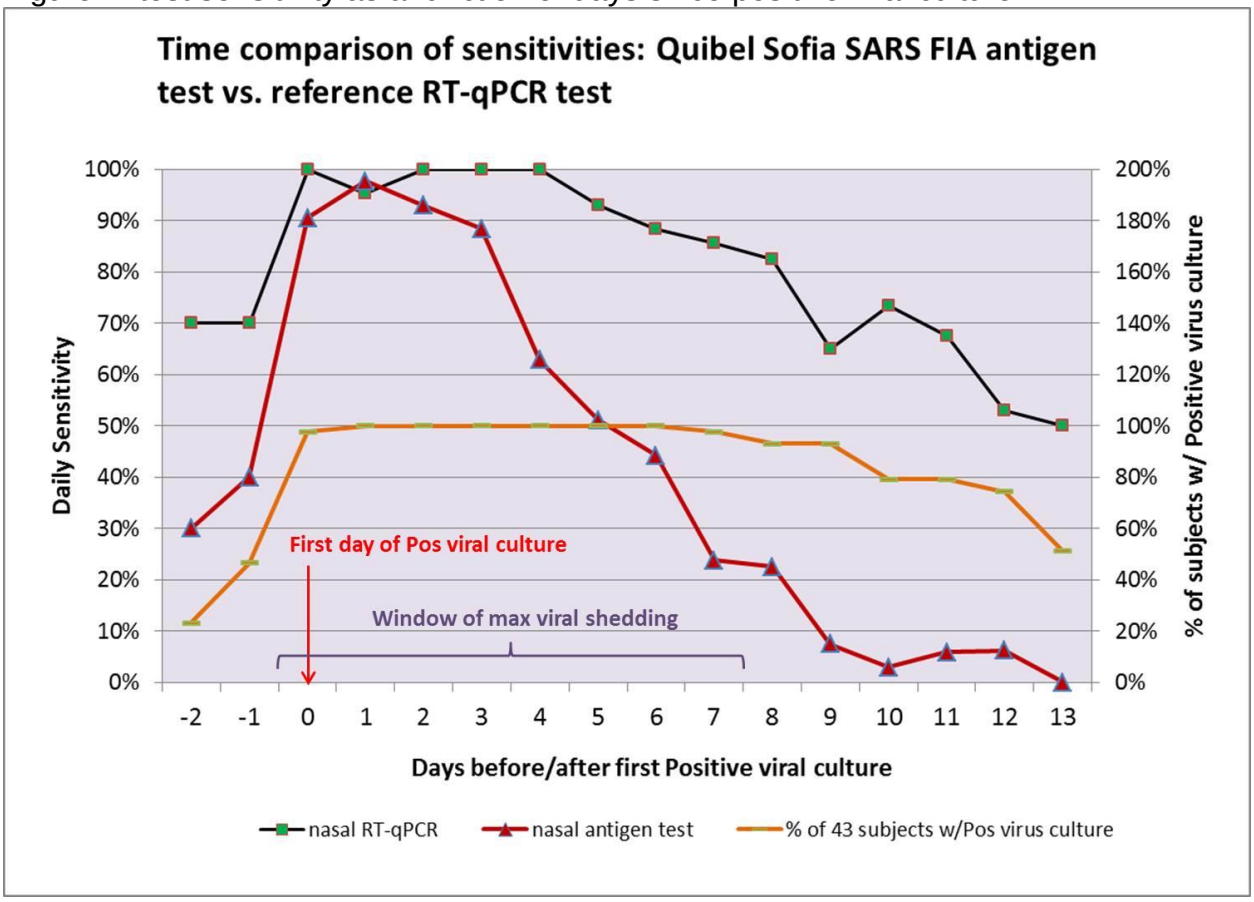
This study is important because, in addition to daily testing with three types of tests, it also ran daily virus cultures from nasal swabs to establish ground truth – whether or not there was enough live virus being shed in the nose to produce a positive culture. Evidence of viral shedding is not evidence of transmission per se. But this study showed that antigen tests, while generally less sensitive, were still able to detect the virus with high probability, at least for several days beginning at the point when the virus was established and had replicated enough to be shed. The study followed 43 newly infected adults (students, staff, and faculty) at Indiana University. The subjects were tested every day for 14 days, with three different tests: antigen with nasal swab (Quidel Sofia SARS FIA), RT-PCR with nasal swab, and RT-PCR with saliva swab. In addition,

their nasal mucus samples were cultured each day to determine if live virus was present. That's a lot of expensive and time-consuming lab work, but it allowed the researchers to demonstrate a correlation between what the tests were measuring and whether a subject was really infected and shedding infectious amounts of live virus.

All 43 subjects had either asymptomatic or mild COVID, and none required hospitalization. They became infected and started shedding culture Pos amounts of virus on different days during the study period. In order to aggregate the test performances across subjects, and to estimate test sensitivities, the study took as "day zero" for each subject, the first day when a nasal swab produced a positive virus culture. This day was used as a "surrogate marker for [beginning of] infectious viral shedding."

I have graphed the resulting aggregate daily test sensitivity data, taken from the paper's supplemental table 1. The graph shows sensitivity data for both the antigen test and the reference PCR test. (Not shown: data from the saliva PCR testing.)

Figure 2. test sensitivity as a function of days since positive viral culture




For this group of 43 infections, there was a four-day window, beginning on day zero, during which the antigen test (red triangles) had an average sensitivity of 92.4% (range of 88.4% - 97.7%). For the two days preceding day zero, the antigen test sensitivity was

much lower: 30% and 40%. On the 4th day after day zero, antigen sensitivity dropped to 63%, and continued to drop steadily lower on subsequent days. But this four day window corresponds to the beginning of the period of max viral shedding, which means that the antigen test has above a 90% probability of giving a Pos result when it matters most – during the first four days of max viral shedding. On the two days preceding that window, the antigen test has at least a 60% probability of giving a false Neg (=1-sensitivity); and similarly, the false Neg rate rises to greater than 50% on day 5 and later. That is not necessarily a bad thing, because the initial two days before day zero, when the antigen sensitivity was lower, were days when these subjects were shedding non-infectious amounts of virus, if any.

The PCR test (green squares), with its higher sensitivity, was detecting the virus 70% of the time, even on the two days prior to day zero. For the next 5 days, beginning on day zero, the PCR test was Pos an average of 98.1% of the time (range 93% – 100%). Of course, even on the days when live virus could be cultured from a nasal swab, there was no guarantee that the person was actively transmitting and infecting others, as that was not measured in this study.

Here is a CDC report that discusses the results of using the Abbott BinaxNOW rapid antigen test in side-by-side comparison testing against an RT-PCR test. In this study, 3,419 paired specimens were collected from persons aged ≥10 years at two community testing sites in Pima County, AZ, back in November, 2020. Viral culture was attempted on 274 of 303 residual real-time RT-PCR specimens with positive results by either test (29 were not available for culture). See: Jessica L. Prince-Guerra, et al, “Evaluation of Abbott BinaxNOW Rapid Antigen Test for SARS-CoV-2 Infection at Two Community-Based Testing Sites — Pima County, Arizona, November 3–17, 2020.” MMWR, 19 Jan 2021.
https://www.cdc.gov/mmwr/volumes/70/wr/mm7003e3.htm

From this CDC report:
*Virus was cultured from 96 of 274 (35.0%) specimens, including 85 (57.8%) of 147 with concordant antigen and real-time RT-PCR positive results, 11 (8.9%) of 124 with false-negative antigen test results, and none of three with false-positive antigen test results. Among specimens positive for viral culture, sensitivity was 92.6% for symptomatic and 78.6% for asymptomatic individuals. When the pretest probability for receiving positive test results for SARS-CoV-2 is elevated (e.g., in symptomatic persons or in persons with a known COVID-19 exposure), a negative antigen test result should be confirmed by NAAT [Nucleic Acid Amplification Test, e.g., RT-PCR, NEAR, TMA, or LAMP].*

*Despite a lower sensitivity to detect infection, rapid antigen tests can be an important tool for screening because of their quick turnaround time, lower costs and resource needs, high specificity, and high positive predictive value (PPV) in settings of high pretest probability. The faster turnaround time of the antigen test can help limit transmission by more rapidly identifying infectious persons for isolation, particularly when used as a component of serial testing strategies.*

The above CDC study is evidence for the theory that antigen tests performed on asymptomatic people are less sensitive than the maker's calibrations; while tests performed on symptomatic people may be more sensitive, and within a few points of the sensitivities of PCR tests. Therefore, in the worked examples for probability of infection in section 6 below, I will assume that an antigen test will have only 70% sensitivity if the person being tested is asymptomatic; but 92% sensitivity if the person being tested has symptoms of flu-like illness.

**5. How to interpret antigen test results: Positive Predictive Value and Negative Predictive Value**

Given all of the foregoing, how should we interpret home antigen test results? How worried should we be about the possibility of a false Neg result? And what should we do if we see a Pos result?

Medical science approaches the interpretation of a test result partially as a statistical problem, which requires the calculation of the test's positive predictive value (PPV) if the result is positive; and negative predictive value (NPV) if the result is negative. Formally, PPV is the probability that you have a disease, given that you have tested Pos using an imperfect test. NPV is the probability that you are not infected, given that you have tested Neg.

These two predictive values depend on two things: the accuracy of the test as noted; and the prevalence of active infections in the local population. COVID prevalence is often tracked and estimated using the local test positivity rate (TPR), which has varied quite a lot from county to county, and from month to month, depending on the severity of local outbreaks. For example, in Santa Clara County (SCC) from 25 Oct to 16 Nov 2021, the reported daily TPR has fluctuated between 1.1% and 1.4%, with 1.4% being the current trailing 7-day average. Source: https://covid19.sccgov.org/dashboard-testing

By comparison, communities and states that have experienced major outbreaks have seen TPRs in the 15%-25% range, where anything above 10% is scary. SCC's 1.4% TPR is considered relatively low, and goes along with the fact that current daily case rates are running less than 10/100k among all adults age 18+, whether unvaxed or vaxed. Daily case rates are running about 6/100K among fully vaxed adults.

**6. Probability of COVID for different testing outcomes**

How do we estimate PPV, the probability that Uncle Bob is infected and contagious, given that he has just tested Pos with a home antigen test? I have summarized some example scenarios in the two tables below, that help to answer that question. For the math geeks, I show derivations of the relevant Bayesian formulas in section 9 at the bottom.

The summary tables assume that the Abbott BinaxNow antigen test is used for the home screening, and that the Roche cobas PCR assay is used, if a second confirmatory test is needed because of a Pos antigen test result. The results would be similar if the Quidel QuickVue antigen test were used as the first test.

The top 4 rows in table 2 correspond to the 4 combinations of symptomology (asymptomatic vs. some symptoms) and test outcome (Pos, Neg), when community prevalence of active COVID infections is 5% (as determined by the test positivity rate). As shown in the studies cited above, symptomology affects sensitivity of antigen tests in a significant way: when testing asymptomatic people, the effective sensitivity is lower than the makers' calibrated value. Here, I have assumed 70% compared to the 84.6% reported by Abbott for the BinaxNOW test to obtain the FDA's EUA. When testing people with flu-like symptoms which are not certain to be from COVID, the sensitivity is actually higher than the maker's EUA value. Here, I have assumed 92%. The bottom four rows in the table are the same, except that prevalence of active infections in the local community is assumed to be 15% (pretty high). For each of the 8 scenarios, I have calculated the post-test probability of COVID. In Bayesian speak, this is the posterior probability, given the data from Test1.

Table 2. Probabilities of COVID after one antigen test

| Symptoms | Community prevalence | Test 1 Name | Test 1 result | Posterior probability of COVID | Sensitivity | Specificity | Conditional probability |
|---|---|---|---|---|---|---|---|
| asymptomatic | 5% | BinaxNOW | Pos | 71.1% | 70.0% | 98.5% | P(C\|T) |
| asymptomatic | 5% | BinaxNOW | Neg | 1.6% | 70.0% | 98.5% | 1-P(C'\|T') |
| some symptoms | 5% | BinaxNOW | Pos | 76.4% | 92.0% | 98.5% | P(C\|T) |
| some symptoms | 5% | BinaxNOW | Neg | 0.4% | 92.0% | 98.5% | 1-P(C'\|T') |
| | | | | | | | |
| asymptomatic | 15% | BinaxNOW | Pos | 89.2% | 70.0% | 98.5% | P(C\|T) |
| asymptomatic | 15% | BinaxNOW | Neg | 5.1% | 70.0% | 98.5% | 1-P(C'\|T') |
| some symptoms | 15% | BinaxNOW | Pos | 91.5% | 92.0% | 98.5% | P(C\|T) |
| some symptoms | 15% | BinaxNOW | Neg | 1.4% | 92.0% | 98.5% | 1-P(C'\|T') |

The post-test probability of COVID in the second row of table 2 may surprise you. Even though I have used a sensitivity of just 70% (false Neg rate of 30%), the post-test probability of COVID is still very low, at 1.6%. Intuitively this is because the combination of lowish prevalence of active community infections, plus the person being asymptomatic, tempers the likelihood of being infected. This effect is seen even in row 6. On the other hand, when the test for an asymptomatic person is Pos, there is a significant difference in post-test probability of COVID (89.2% vs. 71.1%) when prevalence is higher.

The most important takeaway is that if the antigen test is ever Pos, you are looking at the need to isolate, at least until you can get an exculpatory PCR test at a clinic or hospital. I have explored that in table 3 below, by summarizing what happens to the probability of COVID, after both a Pos antigen test, and a PCR test, which can be either Pos or Neg. I am using Roche's S&S values for their SARS-CoV-2 assay, which runs on their cobas family of lab-based systems. Most lab-based PCR tests have similar S&S values.

Table 3. Probabilities of COVID after second test (PCR)

| Symptoms | Prior probability of COVID pre-test2 | Test 2 Name | Test 2 result | Probability of COVID after test2 | Sensitivity | Specificity | Conditional probability |
|---|---|---|---|---|---|---|---|
| asymptomatic | 71.1% | Roche PCR | Pos | 99.2% | 96.4% | 98.0% | P(C\|T1&T2) |
| asymptomatic | 71.1% | Roche PCR | Neg | 8.3% | 96.4% | 98.0% | 1-P(C'\|T1&T2') |
| some symptoms | 76.4% | Roche PCR | Pos | 99.4% | 96.4% | 98.0% | P(C\|T1&T2) |
| some symptoms | 76.4% | Roche PCR | Neg | 10.6% | 96.4% | 98.0% | 1-P(C'\|T1&T2') |
| asymptomatic | 89.2% | Roche PCR | Pos | 99.8% | 96.4% | 98.0% | P(C\|T1&T2) |
| some symptoms | 89.2% | Roche PCR | Neg | 23.3% | 96.4% | 98.0% | 1-P(C'\|T1&T2') |
| asymptomatic | 91.5% | Roche PCR | Pos | 99.8% | 96.4% | 98.0% | P(C\|T1&T2) |
| some symptoms | 91.5% | Roche PCR | Neg | 28.3% | 96.4% | 98.0% | 1-P(C'\|T1&T2') |

The starting prior probabilities in table 3 are the posterior probabilities drawn from table 2, color coded so you can see the connections. In any of the 4 cases from table 2 where the antigen test was Pos, the probability of COVID after a second Pos test via PCR is above 99%, so isolation is mandatory, along with contact tracing. Also very important to see if you can quickly arrange an infusion of one of the monoclonal antibody (mAb) therapies.

If you get a Neg PCR test but have some symptoms (rows 6 & 8), you are in a grey area where the post-test2 probability of COVID is in the 20%-30% range. Especially because of the “some symptoms” aspect, I would still worry about a mild breakthrough case, so I would isolate, and consult with a doctor to see if this merits getting an infusion of mAbs. Assuming the symptoms didn’t get worse, I’d stay home, and start taking a daily antigen test, maybe switching brands from day to day (lower correlation between tests) until I tested Neg for at least two days in a row.

Rows 2 and 4 in table 3 are less problematic, because the post-test probability of COVID is not very great (under 11%). If I were symptomatic, I’d probably isolate and try to get a mAb infusion, but that might be a tough sell because of the Neg PCR test, and a demand that currently exceeds supply for the mAb therapies.

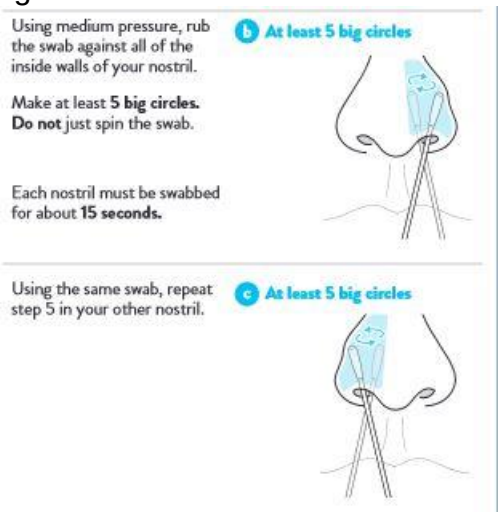
### 7. Using a rapid home antigen test

You may decide to buy some rapid antigen tests at CVS or Walgreens, or perhaps online, and use them for screening at your holiday gatherings. These tests have a shelf life, and the expiration date is printed on the outside of the box. One advantage of buying in person is that you can check that the kit is not expired.

I have heard that the tests are hard to find in some geos, but I was able to find Abbott’s BinaxNOW test kits and Quidel’s QuickVue At-Home test kits at both CVS and Walgreens, near Palo Alto, CA. Both kits were ~$25, with two tests in each kit. Each test comes with a nasal swab, but they are different in how they process the swab to get a sample onto the lateral flow test strip. For either test, you swab yourself in both

nostrils. The good news: no more brain stab - you only need to insert the swab between ½ and ¾ inch up the nostril, as shown in this diagram from the BinaxNOW instructions.

Figure 3. Illustration of swab insertion.




Source: https://www.fda.gov/media/147255/download

**Please be sure to read and follow the instructions, so you don't get an unnecessary false Neg result**.

With the QuickVue test, you swirl the swab around in a test solution pre-packaged in a small vial and let it soak for 1 minute. Remove and discard the swab, then drop a small test strip into the solution for 10 minutes. Remove the strip and place it next to the printed guide. If you see a pink line in the result area, the test is Pos.

The BinaxNOW test comes with a small testing card that opens like a book. On the inside, the test strip is glued to one side, and the other side has two small holes over a small well. You have to carefully squeeze 6 drops of solution into one of the holes, then insert the swab into the other hole and push it forward into the area that holds the solution. Rotate the swab 3 times, then close the testing card and seal it so that the test strip is inside and making contact with the part of the swab tip moistened with solution. After you close the card, a portion of the test strip is visible through a slot on the upward-facing side of the card. There should be a pink/purple line in the area marked "Control." After 15 minutes, check the area marked "Sample." If a second pink/purple line has appeared, the test is Pos. if there is no line, the test is Neg. Sometimes the Sample line will be faint, maybe even very faint, but the instructions say that still counts as Pos. You have to examine carefully.

I have used both tests, and I prefer the QuickVue test, due to its simpler mechanics, and slightly faster processing time.

My advice about using these tests is to **make sure that the person doing the swabbing has read the instructions, and knows what they are doing**. If you are the host at a gathering where you have decided that everyone should be tested as they

arrive, maybe it's best if you take on the role of lab tech, and swab everybody else rather than leaving it up to each guest to get it right. Of course this is after you practice on yourself, and have some confidence about executing the steps to get a valid result.

Repeating the plus side of antigen tests: they have a small false Pos rate, typically less than 1.5%, which is the same as a good PCR test. Therefore, if someone who is symptomatic (even if vaxed) gets a Pos antigen test result just before joining a holiday gathering, it should trigger isolation and a trip to an emergency care clinic for a confirmatory PCR test, followed by isolation until the PCR test result is known. Holidays are not a good time to expect a rapid turnaround for a PCR test. The processing time is likely to go from less than 24 hours, to 2-3 days due to holiday closures and reduced staffing in testing labs.

**Test timing**

It is pretty well documented that the window of contagiousness if you have the Delta variant is from 3 to 10 days after an exposure and infection event, with peak viral shedding between days 4-7. This matters in two ways: behavior of guests for the 7-10 days prior to gathering; and timing of rapid antigen tests. The best time to test is the day of the gathering, preferably before people arrive, and anyway before everyone goes masks off. This maximizes the chance of detecting an infection where someone has just started shedding virus, but is still asymptomatic. This would typically be 3-5 days after being exposed.

But note, testing on the day - if it is the only test - can be testing too late. The antigen tests have that 4-day window of maximum sensitivity, so there is the risk of testing too late to catch max viral shedding. For example, if someone has been exposed and infected 8-9 days earlier, there is a good chance that they have already passed through the phase of peak viral shedding, especially if they are asymptomatic, but may still be able to transmit. So in addition to testing on the day, it is important to know how recently the person was engaging in a high risk activity, or traveling through a community with high TPR – and the worst scenario is that it was a little over a week ago. More recent (4-6 days ago) is actually better, in terms of minimizing the chance of a false Neg result.

**8. Some media articles discussing antigen tests and how to use them**

Here are some recent articles in the NYT and The Atlantic that discuss the use of home antigen tests. These don't get into the math, but are easy reads if you don't care about the details of how to interpret the results, or why the accuracy of antigen tests is better than the manufacturers' specifications would lead you to believe. See:

Tara Parker-Pope, "How to Use Rapid Home Tests (Once You Find Them)." NYT, 10 Nov 2021.
https://www.nytimes.com/2021/10/07/well/live/covid-rapid-at-home-test.html?campaign_id=9&emc=edit_nn_20211124&instance_id=46164&nl=the-morning&regi_id=56024610&segment_id=75214&te=1&user_id=2bd5bb588c3b4cacdc3a2208e4d9ce2d

Katherine J. Wu, "COVID Tests Weren't Designed for This." The Atlantic, 23 Nov 2021.

https://www.theatlantic.com/health/archive/2021/11/coronavirus-testing-still-confusing/620783/
A bit negative. Katherine normally does a great job of explaining complicated topics, but this article makes it sound more complicated than it really is.

David Leonhardt, "Turkey Without Covid. A guide to using rapid tests." NYT, 24 Nov 2021.
https://www.nytimes.com/2021/11/24/briefing/thanksgiving-covid-rapid-test.html

**9. The math behind positive predictive value (PPV) and NPV**

The math is based on Bayesian inference, which makes use of Bayes' Rule of conditional probability. Bayes' Rule (alternatively called Bayes' Theorem) is named for Thomas Bayes (1701 - 1761), an English statistician and Presbyterian minister.

We need some probability notation to show how Bayesian inference works. Let:
C = the event that you really have COVID (and C' = event you're not infected)
T = the event that your COVID test is Pos (and T' = event that your test is Neg)
And:
P(C) = the probability of event C
P(T) = the probability of event T

Predictive value is by definition the conditional probability that you have COVID, given that you have a test result, which can be Pos or Neg. There are two different formulas, one for PPV and one for NPV, depending on whether the test result is Pos or Neg. I'll first develop the formula for the case that the test is Pos. In probability notation, we say that PPV = P(C|T), the probability that you have COVID given a Pos test result. We will make use of two other conditional probabilities that allow us to incorporate knowledge of the test's accuracy parameters, sensitivity and specificity:

P(T|C) = Prob that you test Pos, given you have COVID = true Pos rate, aka test sensitivity
P(T'|C') = Prob that you test Neg, given you don't have COVID = true Neg rate, aka test specificity

People often think of a test's accuracy in terms of its false Pos and false Neg rates, so also note that:
false Neg rate = 1 - seNsitivity
false Pos rate = 1 - sPecificity

**Bayes' rule**
Bayes' Rule, as it applies to a Pos test result:

P(C|T) = P(T|C)*P(C) / P(T) = (Sensitivity*Prior Prob(C))/P(T)

So the conditional prob that you have COVID, given you test Pos, is determined by:
- the probability you Test Pos, given you have COVID (the test's sensitivity);
- the pre-test probability you have COVID (in Bayesian inference, this is known as the Prior probability); and
- the probability of a Pos test (which depends on both sensitivity and specificity)

To see this third point, we expand P(T) using the law of total probability on T:

P(T) = P(T|C)*P(C) + P(T|C')*P(C') = (Sensitivity*Prior) + P(T|C')*P(C')

If we rewrite the second term, we can substitute the test's specificity:

P(T) = (Sensitivity*Prior) + (1 - P(T'|C') )*(1 - P(C)
= (Sensitivity*Prior) + (1-Specificity)*(1-Prior)

Combining all of this, we get the formula for PPV in the event of a Pos test result:

**PPV = P(C|T) = (Sensitivity*Prior) / [ (Sensitivity*Prior) + (1-Specificity)*(1-Prior) ]**

In Bayesian inference, the estimate PPV is referred to as the posterior probability of having COVID, given a positive test.

In the event that the test result is Neg, we want to know the probability of not being infected given that Neg test result. This is referred to as the negative predictive value (NPV). In probability notation, NPV = P(C'|T'), and Bayes' Rule says:

P(C'|T') = P(T'|C')*P(C') / P(T') = specificity*(1-Prior) / P(T'), where:

P(T') = P(T'|C')*P(C') + P(T'|C)*P(C) = specificity*(1-Prior) + (1-sensitivity)*Prior

Combining all of this, we get the formula for NPV in the event of a Neg test result:

**NPV = [specificity*(1-Prior)] / [specificity*(1-Prior) + (1-sensitivity)*Prior]**

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Happy holidays, and test to stay safe at gatherings!

BGL