COVID Update 140. Rapid antigen testing: Two tests are better than one

In Update 139, I was proposing community test positivity rate (TPR) as a proxy for the local prevalence of active contagious COVID infections. In my example calculations, I chose to use some large values (5% and 15%) for TPR, as Bayesian priors. And while prevalence of contagion and TPR are correlated, TPR can overstate the pre-test probability of being infected in the general population. So with apologies, I need to walk that idea back.

In this Update, I'll discuss some better alternatives for choice of pre-test prior, based around daily new cases per capita, with some worked examples for Santa Clara Co., CA, Middlesex Co., MA, and a few others. I also want to recommend a better testing scheme to use, prior to attending holiday gatherings. It calls for two rapid home antigen tests in advance of an event. I have flowcharted that scheme and included the Prob(COVID) estimates following each test, so you can see how your likelihood of being infected changes, depending on the test results.
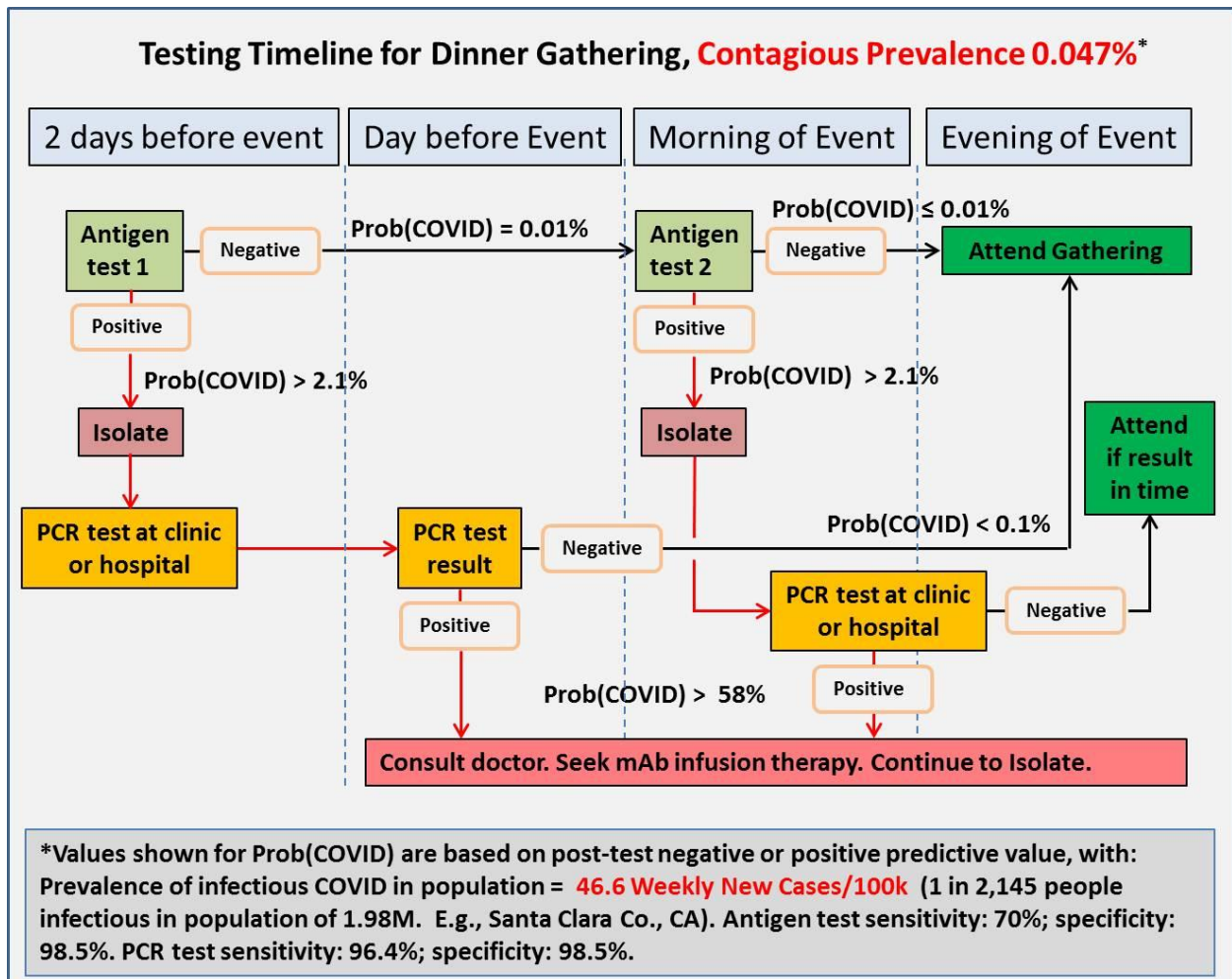
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1. Why two antigen tests are better than one, before attending gatherings
In the diagram below, I show a double antigen testing strategy that is more effective than just taking a single antigen test before leaving for a gathering. The recommended approach is to take the first home antigen test two days prior to the event. If that test is Neg, then wait until just prior to leaving for the event, and take a second antigen test. If either test should be Pos, you need to isolate, at least until you can get a confirmatory/exculpatory PCR test at a walk-in clinic, Dr.'s office, or hospital.

There are two good reasons to take the antigen tests two days apart like this: First, as I explained in the last Update (U139), antigen tests are actually quite good at detecting the presence of contagious virus early in the window of the 3-5 days of peak viral shedding which happens beginning 3-4 days after exposure and infection. But if you only test once, you may be testing too early (prior to onset of shedding); or you may be testing too late - in the latter part of the shedding window, at a point where you are still infectious, but an antigen test is not sensitive enough to detect viral N-proteins. By testing two days prior to the gathering, and again on the day of it, at least one of the two tests will fall in the window of max viral shedding, and you are likely to catch it with an antigen test.

Testing Timeline for Dinner Gathering, Contagious Prevalence 0.047%[*]

| 2 days before event | Day before Event | Morning of Event | Evening of Event |

Antigen test 1 — Negative — **Prob(COVID) = 0.01%** → Antigen test 2 — Negative — **Prob(COVID) ≤ 0.01%** → **Attend Gathering**

Antigen test 1 — Positive — **Prob(COVID) > 2.1%** → Isolate

Antigen test 2 — Positive — **Prob(COVID) > 2.1%** → Isolate

Isolate → PCR test at clinic or hospital → PCR test result — Negative — **Prob(COVID) < 0.1%** → Attend if result in time

PCR test result — Positive

Isolate → PCR test at clinic or hospital — Negative → Attend if result in time

PCR test at clinic or hospital — Positive

Prob(COVID) > 58%

Consult doctor. Seek mAb infusion therapy. Continue to Isolate.

*Values shown for Prob(COVID) are based on post-test negative or positive predictive value, with: Prevalence of infectious COVID in population = **46.6 Weekly New Cases/100k** (1 in 2,145 people infectious in population of 1.98M. E.g., Santa Clara Co., CA). Antigen test sensitivity: 70%; specificity: 98.5%. PCR test sensitivity: 96.4%; specificity: 98.5%.

The second reason to test two days early is that you may get a false Pos on the first antigen test. Antigen tests generally have very good specificity, around 98.5%, which means that they have a low false Pos rate: 1.5%, which is as good as many PCR tests. So a false Pos on an antigen test is rare, but they do happen. Ask Governor Mike DeWine, of Ohio (covered back in U74, 9 Aug 2020). By leaving yourself two days until the event, if you get a Pos result on the first antigen test, you may be able to quickly get a PCR test to help determine if that result was a true Pos or a false Pos. If it turns out to be a false Pos (i.e., the PCR test comes back Neg, and you are asymptomatic), you might find that out in time to still attend the gathering.

For each test outcome, the diagram shows a post-test probability that you are infected. These probabilities are denoted Prob(COVID). As I explained in the last Update (U139), the Bayesian estimates for these probabilities depend not only on the test accuracies, but also on the prevalence of contagious people in the community to whom you are exposed. The probabilities in this diagram are based on a relatively low contagious prevalence value of 0.047%. That value represents an estimate for current prevalence of contagious individuals in Santa Clara County, CA. It is based on the ratio of recent weekly new cases (= 923) to the county population, 1,980,000 residents.

This number for contagious prevalence is an estimate. In the sections below, I'll explain why it is a plausible starting point, but also why such a county-level statistic may not be accurate for your personal circumstances, which include your vax status, family housing circumstances, work environment, social circle, lifestyle, and adherence to public health behaviors like distancing and masking. In particular, if you are fully vaxed and boosted, and mostly are still living in a bubble, with no air travel, and minimal contact with strangers in crowded indoor venues – and always with good masking when you must, then your pre-test prior for COVID may be considerably less than the county-level statistic for your county.

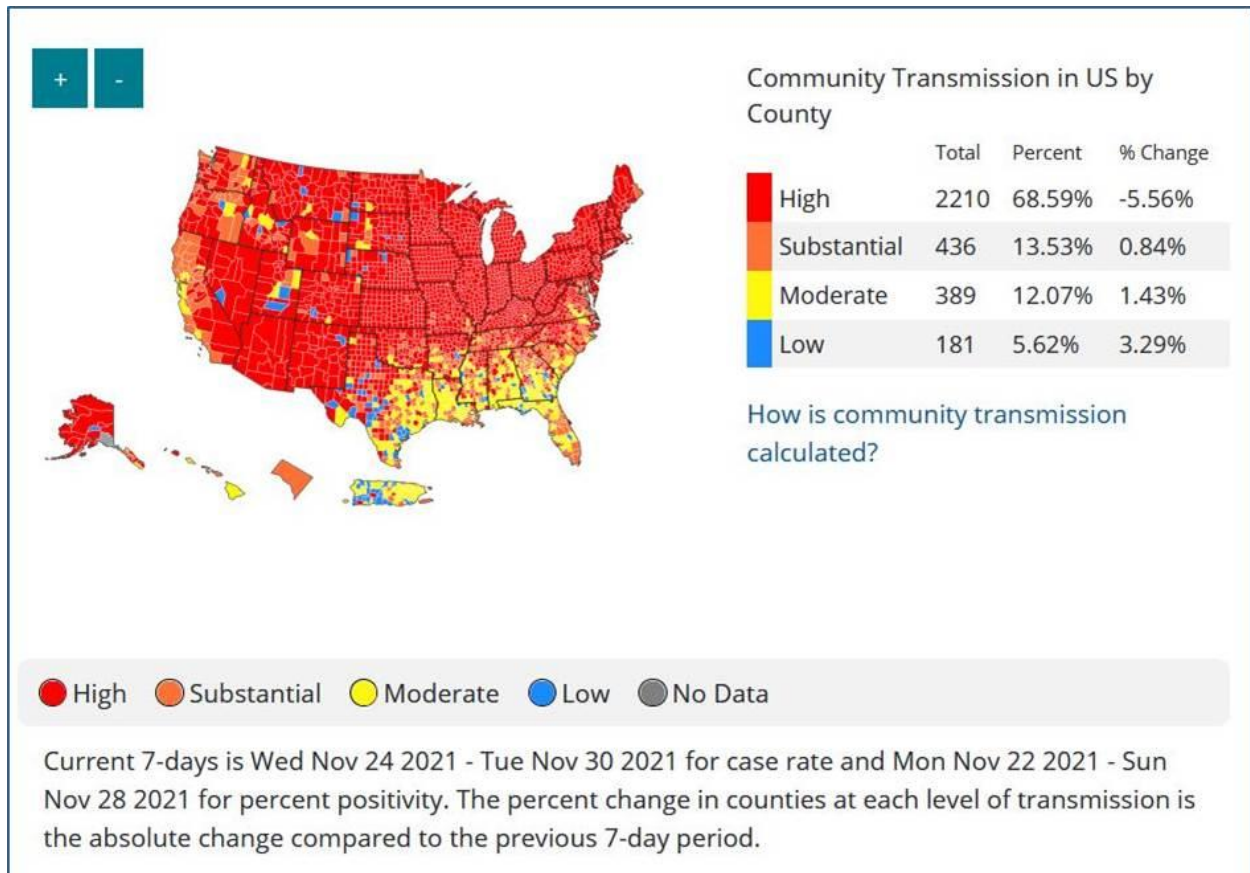**2. Choosing a value for pre-test probability that you have COVID**
The premise for choosing a community-based prior based on the local case rate is this: If you live in a geo where weekly new cases per capita (metric: WNC's/100k) are very high, your chances of coming into contact with an infectious person are greater than if you live where local case rates are low. In that connection, the CDC maintains an interactive site where they track COVID statistics for every county in the U.S., plus protectorates like Puerto Rico. See: "COVID-19 Integrated County View."
https://covid.cdc.gov/covid-data-tracker/#county-view

At this site, you can enter a state and county, and see many current statistics on cases, testing, vaccinations, and hospitalizations. Handy if you want to check the situation in a county that doesn't maintain its own COVID Dashboard. In addition to the statistics, the CDC gives each county a Transmission Risk score: Low, Moderate, Substantial, or High. The score is based on two statistics: Weekly New Cases/100k (summed over a recent 7-day period); and the test positivity rate (TPR), as determined by testing with nucleic acid amplification tests (NAATs, most of which are PCR tests). Here's the scale:

Determining Transmission Risk

If the two indicators suggest different transmission levels, the higher level is selected

	Low	Moderate	Substantial	High
New cases per 100,000 persons in the past 7 days*	<10	10-49.99	50-99.99	≥100
Percentage of positive NAATs tests during the past 7 days**	<5%	5-7.99%	8-9.99%	≥10.0%

The CDC score uses the higher of the two metrics, in case the two do not align. As of 1 Dec 2021, there were only 181 U.S. counties where the Transmission Risk was Low. Here is the current CDC choropleth map of the U.S. + Puerto Rico. Generally, it is the weekly new cases (WNCs)/100k that determine the CDC score in the map.

Community Transmission in US by County

	Total	Percent	% Change
High	2210	68.59%	-5.56%
Substantial	436	13.53%	0.84%
Moderate	389	12.07%	1.43%
Low	181	5.62%	3.29%

How is community transmission calculated?

● High ○ Substantial ○ Moderate ○ Low ○ No Data

Current 7-days is Wed Nov 24 2021 - Tue Nov 30 2021 for case rate and Mon Nov 22 2021 - Sun Nov 28 2021 for percent positivity. The percent change in counties at each level of transmission is the absolute change compared to the previous 7-day period.

I have tabulated some of the CDC's COVID statistics and calculated others, for nine U.S. counties, in table 1 below. Before I get into the pre-test prevalence discussion, a side note on testing. I have included a simple testing ratio in table 1, which is: (population) / (NAAT tests performed over last 7 days). In the table, I call this the "virtual percentage" of the population that has received a test in the most recent week. It is notable that Manhattan and Middlesex Co., MA, are doing a lot of testing in response to rising cases and hospitalizations. They are administering the equivalent of one test for every 10 residents, per week, but of course some people are being tested multiple times, so it's not quite that good.

Note also that, in spite of misinformation to the contrary, testing more does NOT necessarily lead to a higher positivity rate. Manhattan is testing twice as much per capita as is San Mateo Co., CA; but the Test Positivity rates are comparable, at 1.65% and 1.4%. By comparison, Genesee Co., MI, which includes the city of Flint, is not doing enough testing in the face of rising cases. This is also the story in Detroit and other cities in Michigan – and their hospitals are overflowing again.

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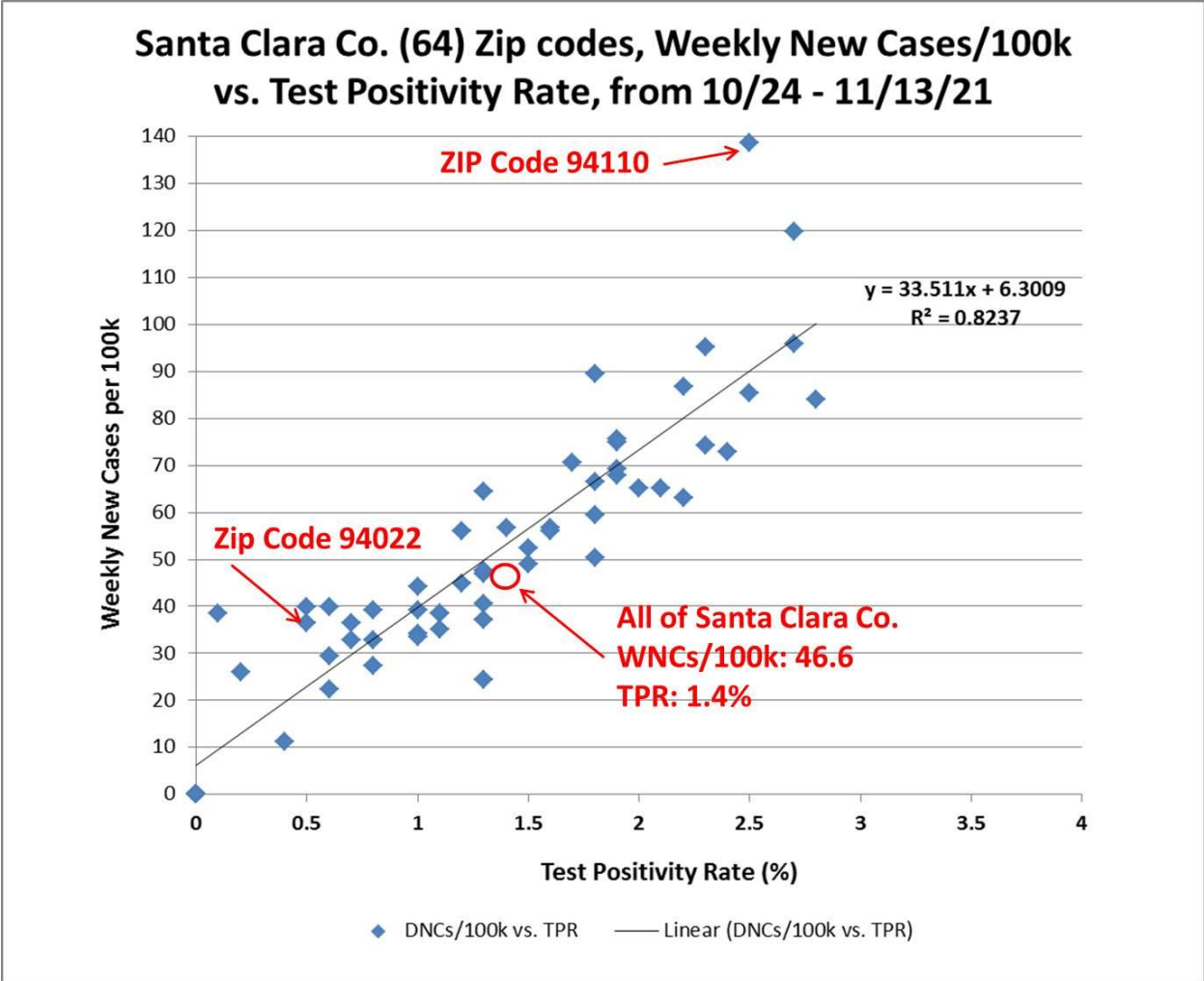
Table 1. Comparison of COVID statistics for nine U.S. counties

Data from CDC: "COVID-19 Integrated County View." 1 Dec 2021
https://covid.cdc.gov/covid-data-tracker/#county-view

	Victoria Co., TX	San Mateo Co., CA	Santa Clara Co., CA	Broward Co., FL	Los Angeles Co., CA	(Manhattan) New York Co., NY	Middlesex Co.,MA	Morris Co., NJ	Genesee Co., MI
CDC's Level of Community Transmission	Low	Moderate	Moderate	Substantial	Substantial	High	High	High	High
County population	92,084	766,573	1,980,000	1,952,778	10,039,107	1,628,706	1,611,699	491,845	405,813
% of population 65+	16.6%	16.6%	13.9%	17.1%	14.1%	17.0%	15.7%	17.6%	18.0%
Weekly New Cases (last 7 days)	9	262	923	1,077	5,935	1,913	3,162	1,063	2,214
WNCs per 100k pop	9.8	34.2	46.6	55.2	59.1	117.5	196.2	216.1	545.6
Test Positivity (last 7 days)	2.88%	1.40%	1.40%	2.96%	1.02%	1.65%	2.44%	6.53%	24.08%
NAAT Tests performed (last 7 days)	342	37,339	104,716	50,286	573,749	146,981	167,998	16,359	11,255
virtual % of pop tested (last 7 days)	0.4%	4.9%	5.3%	2.6%	5.7%	9.0%	10.4%	3.3%	2.8%
(est.) prevalence of contagious cases	0.010%	0.034%	0.047%	0.055%	0.059%	0.117%	0.196%	0.216%	0.546%
SVI	0.7834	0.265	0.3557	0.5844	0.7682	0.5510	0.2264	0.1201	0.6624
COVID Com'ty Vulnerability Index	0.53	0.1	0.15	0.6	0.49	0.32	0.3	0.1	0.38
% total Pop fully vaxed	45.3%	75.0%	77.4%	65.3%	40.2%	75.8%	71.8%	71.2%	46.7%
% Pop 12+ fully vaxed	54.4%	85.9%	89.5%	75.6%	74.4%	84.2%	81.9%	81.6%	54.6%

Current 7 day ranges — Case rate data: Wed 24 Nov - Tue 30 Nov 2021
Test Positivity data: Mon 22 Nov - Sun 28 Nov 2021

In table 1, the row labeled "prevalence of contagious cases" is my calculation, which is just computing the ratio of weekly new cases to county population. I think of it as an estimate of the percent of county residents who are currently infectious; and I am using that statistic in my Bayesian formulas, to generate Prob(COVID) estimates (examples below). But, you say, don't we expect that most of the people who are sick enough to have gotten a Pos PCR test are either in isolation, or in the hospital, so not adding to transmissions in public? Yes, but counterbalancing that we know that historically between 30% - 50% of all cases are asymptomatic, and most of these are never tested. And in areas where the vaccination rate is high, asymptomatic or mildly symptomatic cases are even more likely to be prevalent – and go undiagnosed or tested. On balance, I believe that infected people who go untested are probably more numerous than those who do get tested. So I'm going with the idea that asymptomatics and pauci-symptomatics who are still out and about, will offset the fact that many PCR Pos people are not in the public mix.

There is also the fact that the mixing of people in a geo the size of a populous county is far from homogeneous. People live in neighborhoods, their kids go to particular schools, the parents and kids socialize with a small network of friends, etc. All of this contributes to heterogeneity between neighborhoods within a county, and ultimately to uneven spreading of cases in different towns and neighborhoods.

Here is an example of that, from Santa Clara County. Believe it or not, the county posts time series data for the three-week average case rate and the test positivity rate for each of the 64 postal zip codes in SCC. From table 1 above, the recent trailing 7-day average TPR for SCC is 1.4%; and the WNCs/100k = 46.6. In the figure below, I have plotted a scatter diagram of WNCs/100k vs. TPR, averaged over the recent 3-week period from 24 Oct – 13 Nov 2021.

Santa Clara Co. (64) Zip codes, Weekly New Cases/100k vs. Test Positivity Rate, from 10/24 - 11/13/21

$y = 33.511x + 6.3009$
$R^2 = 0.8237$

Most of the town of Los Altos lies within zip 94022 (TPR = 0.5%; WNCs/100K = 36.4). These statistics are pretty different from zip 94110 (TPR = 2.5%; WNCs/100k = 138.6). Zip 94110 includes San Jose airport and surrounding neighborhoods. A side note: this data shows the expected high correlation between case rates and test positivity rates (R^2 = .82). But zip 94110 is an example of where the correlation breaks down.

What about people who are more cautious than the average bear, living in a "careful bubble," and doing an excellent job of following safe public health behaviors? For them, even a local town rate (WNCs in town)/(town pop) may be too large to use as a prior estimate for pre-test Prob(COVID). At whatever scale of geo you choose: county or town (I would not use state-level), the WNCs/(geo population) are measuring the infections that result among all people in the geo, and they will have a spectrum of individual behaviors that vary across at least these dimensions:
 - vaxed vs. unvaxed
 - masked vs, unmasked
 - work exposures (public-facing vs. outdoor vs. office)
 - leisure exposures (restaurants, bars, sporting events, concerts)
 - heterogeneity vs. homogeneity of social networks

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Bottom line, based on your vax status and behavior, you may choose to adjust your pre-test transmission risk downward from the county-level statistic. In the next two sections, I'll show some calculations for three of the counties in table 1 above, and I'll stick with the county-level statistics, so you can see how that affects the probabilities.

3. For selected counties: probability you are infected, given post-test results
Here are some Prob(COVID) results for the counties of Santa Clara (SCC), Middlesex in MA, and Genesee in MI. These counties span the range of prevalence of contagiousness across the nine counties in table 1.

Prob(COVID) comparisons, pre-test and post test

	SCC	Middlesex	Genesee
pre-test prior (county-level prevalence)	0.05%	0.20%	0.55%
If Antigen test 1 Neg	0.01%	0.06%	0.17%
If Antigen test 1 Pos	2.13%	8.40%	20.38%
If Antigen test 1 Neg, and Antigen test 2 Neg	< 0.01%	< 0.06%	< 0.17%
If Antigen test 1 Neg, and Antigen test 2 Pos	2.13%	8.40%	20.38%
If either Antigen test is Pos, and PCR test Neg	0.08%	0.34%	0.93%
If either Antigen test is Pos, and PCR test Pos	58.3%	85.5%	94.3%

In all three counties, we start off with a pre-test prior less than 1%; but Genesee's prior is a factor of 10 higher than SCC's. Two Neg antigen tests result in an estimate for Prob(COVID) that is less than 0.2% for all counties, so pretty safe to join a gathering without worrying that you might be bringing a contagious infection.

If either antigen test is Pos, you should take a confirmatory PCR test. If that test is Neg, you can be pretty confident that the antigen test was a false Pos, and you can join a gathering without worrying. However, if you are in a county or town with a high prevalence like Genesee Co., your Prob(COVID) after the Neg PCR is just under 1%. Maybe this should give you pause if you are joining family members or friends who are high risk due weakened immune systems, or inability to get vaccinated.

If the confirmatory PCR test is Pos, you should stay home, isolate, and consult a doctor about quickly scheduling an outpatient infusion of a monoclonal antibody (mAb) treatment. In SCC, with a probability of COVID around 58% after a Pos PCR test, your doctor might advise just isolating, if you are asymptomatic. I myself would find that too risky, and would still try to arrange a mAb treatment. With the higher probabilities after a Pos PCR test for Middlesex (>85%) and certainly for Genesee (>94%), I would be much more insistent about the mAb treatment, if you can get it.

4. Availability of monoclonal antibody and antiviral treatments

In Update 136 (4 Oct 2021), I wrote that the U.S. Department of Health and Human Services has a website where they are posting infrequent updates concerning the availability of mAb treatments. See "Important Updates: Monoclonal Antibody Therapeutics."
https://www.phe.gov/emergency/events/COVID19/therapeutics/Pages/updates.aspx

In the HHS bulletin dated 13 Sep 2021, HHS announced that distribution for COVID-19 monoclonal antibody therapeutics was transitioned from a direct ordering process to a state/territory-coordinated distribution system. That update also listed a quota of doses by state. I have not seen HHS posting anything further on that issue, and hopefully things have gotten better in terms of supply at the state level. Back then, HHS was indicating that the distribution system had a weekly supply of 17,880 doses of the bamlanivimab+etesevimab therapy; and 158,580 doses of the Regn-COV therapy. Disproportionate amounts were being allocated to the states with the most cases of Delta. At this time, checking with your doctor is the best suggestion I can offer.

The drama around this should go way down next year, once we have FDA EUAs and availability of the oral antiviral treatments from Merck (molnupiravir) and Pfizer (Paxlovid). Molnupiravir was approved for use in the U.K. on 4 Nov 2021:
https://www.bbc.com/news/health-59163899

The availability of antiviral pill therapies in the U.S. looks likely for some time in calendar Q1, 2022. The FDA granting of EUA for molunpirvir seems possible soon, although the advisory committee vote was split, 13-10, in favor of approval. See: Matthew Herper, "FDA panel narrowly recommends authorization of first antiviral pill to treat Covid-19." statnews, 30 Nov 2021.
https://www.statnews.com/2021/11/30/fda-panel-narrowly-recommends-authorization-of-merck-covid-pill-after-day-of-tense-discussion/

Pfizer applied to the FDA for Paxlovid EUA in mid-November. The FDA is expected to rule on this application before the end of 2021. See: "Pfizer Seeks Emergency Use Authorization for Novel COVID-19 Oral Antiviral Candidate." Pfizer.com, 16 Nov 2021.
https://investors.pfizer.com/investor-news/press-release-details/2021/Pfizer-Seeks-Emergency-Use-Authorization-for-Novel-COVID-19-Oral-Antiviral-Candidate/default.aspx

5. Example calculations for post-test probabilities using Bayesian inference
For a typical rapid antigen test:
  sensitivity = 0.70 (lower than antigen test maker's spec of ~.85, if asymptomatic)
  specificity = 0.985

Here are some calculations using the data for Santa Clara Co.:
weekly cases = 923
SCC population = 1,980,000

estimated prevalence of contagious people = 923/1,980,000 = 0.047%
I use this value as the first prior, in the Bayesian inference process.

Prob(COVID after a Neg antigen test) = 1 – Prob(no COVID after a Neg test) = 1 - negative predictive value (NPV), where:

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

For the SCC data:
  NPV = [0.985*(1-0.00047)] / [0.985*(1-0.00047) + (1-0.7)*0.00047] = 0.9999

And Prob(COVID| Neg antigen test) = 1 - .9999 = 0.014%, pretty small.

Prob(COVID after a Pos antigen test) = positive predictive value (PPV), where:

  PPV = (sensitivity*prior) / [(sensitivity*prior) + (1-specificity)*(1-prior)]

For the SCC data and antigen S&S:
  PPV = (0.7*0.00047) / [(0.7*0.047) + (1-0.985)*(1-0.00047)] = 2.13%
(this is referred to as the posterior1 probability)

In the event that an antigen test is Pos, you need to take a PCR test, and the Bayesian inference process incorporates the result of the PCR test with the same formulas, but switching to the S&S values for the PCR test, and using as the new prior, prior2 = posterior1 probability.

For a typical PCR test, sensitivity = 0.964; and specificity = 0.985.

And **Prob (COVID after Pos antigen test and Pos PCR test)** = PPV2, where:

  PPV2 = (sensitivity*prior2) / [(sensitivity*prior2) + (1-specificity)*(1-prior2)]

For the SCC data and PCR sensitivity and specificity:

  PPV2 = (0.964*0.0213) / [(0.964*0.0213) + (1-0.985)*(1-0.0213)] = 58.3%

6. Summary
I hope that you will use the two-test antigen test protocol in advance of holiday gatherings. This is a very good way to ensure that you or another guest do not unwittingly bring a contagious case of asymptomatic or mildly symptomatic COVID to a gathering of family and friends. The post-test probabilities in this Update are meant to give you a feel for how the testing changes the odds that you are infected, and to convince you that the testing can really work to catch even asymptomatic infections.

Test to stay safe,
BGL

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