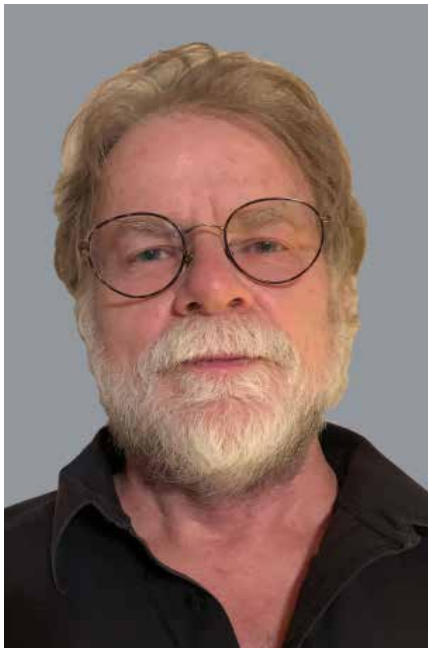

CORO LUX

Covid Lux Redux

Fall 2020
August 30, 2020

By Dr. Joe Alcorn

Executive Summary

• Singing remains among the most effective ways to launch the virus into the air and beyond the 'six-foot' distancing standard. Risks of spreading and of contracting virus clearly decline as distance lengthens, with mask use, and is markedly lower outdoors.

• Choirs cannot practice or perform with complete confidence in their own safety and the safety of the audience until it is possible to be assured no member carries and can communicate the infection.

• We do not yet have vaccine-based immunity or a confident grasp on the details of post-infection immunity. A massive investment in vaccine-based immunity looks promising for 2021 but is not assured.

• Testing singers on the day of practice or performance and excluding those with (presumably) asymptomatic or pre-symptomatic - but contagious - COVID -19 may become feasible in the next few months. Whether the false-negative rate on these tests will be acceptable for the high-risk activity of singing will remain a problem remains to be seen.

• I have written to the manufacturer of 'the Singer's Mask' - the one Brad recommended that makes you look like you have a muzzle, but I have not heard back yet on its specs or construction.

(See next page for the full report)

CORO LUX

Covid Lux Redux

Fall 2020

Virus fundamentals

Taxonomy: Elsewhere on this site are earlier reports on choral singing and SARS-CoV-2, the novel member of the Corona virus family that is responsible for the illness we call COVID -19, the Corona Viral Disease that emerged in 2019. This virus differs from the other human-infecting Corona Viruses in the same way a Sperm Whale differs from a Killer Whale. Both are members of the Toothed Whale Family but if you are a squid or a seal, you DEFINITELY want to be able to tell them apart - and distinguish them from Dolphins while you're at it. Taxonomically speaking, creatures in the same family share obvious similarities and substantial overlap in their genetic material. But they are clearly different enough that a defense against one isn't very likely to work for the others.

Those other Corona Viruses include the virus causing SARS (the original Severe Acute Respiratory Syndrome) called 'SARS CoV' that killed nearly 800 people around the world in 2003 as well as the virus causing MERS (Middle East Respiratory Syndrome) and several viruses responsible for typical and relatively benign Upper Respiratory Infections - the Common Cold. This brief taxonomy will be relevant to understanding some of what follows. A brief review of viral "behavior" is also pertinent.

The Virus: SARS-CoV-2 virus is a delivery vehicle. It has to 'dock' with a human cell to deliver its payload - which is basically the Plan for viral replication. The Plan is encoded in its RNA (whereas Humans and the animal kingdom use DNA master blueprints) but the machinery to translate that plan into the construction of more protein capsules and more RNA can't be accomplished without the energy and materials found in the living cell. The virus has to hijack this machinery to replicate.

In order to dock, a unique protein (the "spike protein") on the surface of SARS CoV-2 has to interact with a particular receptor on the cell. It really IS much like docking with the Space Station. The spike protein happens to fit precisely into this **A**ngiotensin- **C**onverting **E**nzyme 2 Receptor causing a transformational adjustment in both cell membrane and virus. The cell expects ACE at the door, but instead - SURPRISE! - it's the pirate virus RNA.

It probably takes on the order of 10 minutes for an unopposed virus in contact with the receptor to gain entrance, perhaps ten hours to hijack the machinery for replication, and then somewhere around 3,000 copies of the virus begin to emerge. [1] The cell does not recover. ACE 2 receptors are found naturally in the gut and muscle (including cardiac muscle) and elsewhere, but infection from outside the body seems to begin in the cells lining the respiratory tract, the portal of entry. Once the virus has destroyed respiratory surfaces and provoked inflammation it is not surprising to find it gains access to the bloodstream and can then invade gut and muscle and other cell types.

The Antibody Response: If the newly infected human lives long enough he or she will likely develop Immunoglobulin M and G antibodies that recognize and attach to the virus and if they are truly neutralizing, prevent replication. Without prior exposure and some immune 'memory' of the virus though, the human can be very sick or dead before the intrinsic antibodies have been developed. A vaccine is intended to supply that memory, inducing in this case mostly antibodies in the bloodstream that recognize and attach to that Spike protein to prevent it from fitting into its receptor. Such antibodies can't be expected to prevent all initial respiratory invasion but they appear to be very effective, once they arrive on the scene, shutting down the infection.

The Outcome(s): Obviously if each of the 3,000 daughter-viruses is successful in its own cell-invasion than in ten more hours there are nine million viral particles and in another ten, 81 billion… This also means that if the initial onslaught was ALREADY a million viri, THEN in ten hours you have a billion and in 20 hours a trillion… Clearly to control the virus it is best to intervene early!

I have seen no data to suggest how much damage has to occur before a person feels ill but there are some viruses - like hepatitis C for instance - in which considerable damage takes place before there are any symptoms. (Clinical stories of patients unaware of their low oxygen levels and horribly abnormal lung imaging studies abound with COVID-19.) Presumably in some folks, viral replication sufficient to make the person infectious does not cause injury enough to create symptoms. We'll return later to the question of why there is such variability in clinical disease but regardless, viral shedding and contagion risk appears to be greatest 3-5 days after infection when few people are symptomatic.

Also note that once ensconced in a human, a cohort of SARS CoV-2 is predestined for one of three fates:

1) The immune system quashes the virus, the patient recovers, and that viral lineage is kaput.

2) The immune system fails to quash the virus, the patient dies, and that viral lineage is kaput.

3) Regardless of immune response, some of the viral particles are expelled, find another human respiratory tract, and start the process all over again.

Implications: From just this brief review of some basics it is clear that a) the virus cannot replicate on a surface or in the air, or anywhere but inside the human cell and b) people can be capable of infecting others even if not themselves feeling ill, and most importantly c) if the virus is prevented from access to uninfected human cells, the disease stops.

Furthermore, in the same way that the prevention of one human infection early in a pandemic may mean thousands fewer infections later, even ten fewer successful hijackings at the time of initial infection mean ten million fewer virons in that respiratory tract 20 hours later.

If there is one overall lesson from the inexorable math of logarithmic growth, it is that the sooner you act, the more effective the action.

If at this point you want to skip any further bloviating then there are some cogent general references worth review including a useful animation on masks; then stick to the executive summary. Whereas if you are a COVID-19 News Junky then review previous postings and read on!

General references

1) https://www.yalemedicine.org/stories/2019-novel-coronavirus/
2) https://www.statnews.com/2020/08/17/what-we-now-know-about-covid19-and-what-questions-remain-to-be-answered/
3) https://www.vox.com/21296067/coronavirus-covid-symptoms-superspreaders-superspreading-contagious-bars-restaurants

(click on the image (left) for an imbedded explanation of Mask function)

COVID and Saber-metrics

Intro: “Sabermetrics” comes from the **S**ociety of **A**merican **B**aseball **R**esearch. The term has been adopted for other sports as well and loosely speaking represents a close analysis of the processes of a sport, looking for stable probabilities that might be leveraged to increase the chances of winning. For instance, if you analyze every drive that LeBron James has ever made to the basket you might find out (and I’m making up the numbers) that when he goes to his right he averages 1.7 points per drive but if he goes to his left, only 1.6. If you then set up your defense to force him to his left for 20 drives, you can expect two fewer points than he might have made with his preferred pathway. And that could be the ball game. Sabermetrics arose in baseball (anybody seen Brad Pitt as Billy Bean in “Moneyball”?) but are applied even to soccer - *o jogo bonito* that I’ll use as a reference here - measuring ‘touches’ of the ball, ball control time, results of passes to various positions and players and so on in order to unearth what might be hiding beneath the game’s surface - tendencies of teams and players that might be exploited to increase the odds of success.

DEEE-fence: What if we think this way about SARS CoV-2 and its Goal of replication? What does it take for the virus to be successful and how would understanding this help us set up a Defense to lower its chances of scoring?

To begin with. nobody knows the “exact” number of viri that have to be incorporated into human cells to sustain a new infection (let alone how many viri have to be inhaled to reliably deliver that number to the ACE 2 receptors) but it is probably in the hundreds for this virus.[2] For our purpose let’s consider a successful infection to be a Goal. Which means getting a sufficient dose of SARS CoV-2 from an infected person’s respiratory tract into contact with enough ACE 2Rs of an uninfected person to establish replication. How do you lower the odds of this happening?

The Score: We can't do much to alter our **internal defense** - from our nose on into the interior - so Sabermetrics doesn't help us much here. There are ACE 2 Receptors on all the cells lining the alveoli of the working lung but also the branching airways or bronchi as well as the epithelium lining the nose and pharynx. The greatest number of ACE 2R-bearing cells in the respiratory system are the air sacs or alveoli but the density of receptors on the cell surface doesn't seem to be appreciably different among these compartments.[3]

On the other hand, more nearly laminar air flow in the nostrils may be a very different environment for docking than the stillness of the alveoli - not further discussed here but the point is that we do not yet know if there are regions or features of the respiratory tract that favor or discourage viral/receptor interaction.[4]

There is some evidence with SARS virus that the greater the number of receptors the more easily the cells are infected.[5] But to get to these receptors the virus will have to ***run the gauntlet*** of nasal hair and entrapping mucus, of beating cilia driving that mucus up and out, as well as the distinct immunologic system lining the respiratory tract and lungs - including the class of Immunoglobulins known as ***IgA***. These antibodies are active on the inner respiratory surface outside of the blood stream or cell. The role in SARS Co-V-2 surface immunity is uncertain but by attaching to the Spike protein (in the same way as blood-borne vaccine-induced antibodies) they too can block the docking of the virus - which would make them a potentially important part of successful immune response.[6]

But furthermore, since their activity takes place along the surface of the airways where the virus is trying to dock (to gain entrance to the layer of cells that make that lining), it is theoretically possible that this virus, which is what is expelled in a sneeze or a *sforzando* to cause new infections, could be IgA-capped, unable to dock, and therefore rendered non-infectious when it was sneezed coughed yelled or yodeled back into the atmosphere! This class of antibodies is probably amenable to parenteral vaccine induction,[7] but there COULD be an advantage to a vaccine delivered directly to the respiratory tract by inhalation 'teaching' the respiratory system directly to rev up production of these IgA-type antibodies that glom onto the Spike protein so it cannot dock ….

Clearly there are enough variables here that it seems likely some people will defend internally better than others. And indeed, there are a number of reports suggesting variability in the immune response influences disease severity.[8] It seems likely that similar subtle differences in individual immune systems may be responsible for variability in the ease of infection or perhaps influence the number of viri it takes to cause an infection.

Externally, while there is no infallible defense on the pitch any more than for SARS CoV-2, there may be tendencies we CAN manipulate to our advantage…

For instance, it would be very rare to lose a game in which your opponent never took a shot on goal. So, a simple starting strategy might be to keep all the viri out of the box - out of that area right in front of the net from which scoring is easiest. You don't have to know exact numbers to recognize that the fewer viral shots on goal, the lower the chances it will score.

Of course, in soccer you can see the ball and you can assign a defender to the players with the most accurate long range and accurate delivery. What are you defending with COVID -19? It seems to be mostly if not exclusively inhaled virus.

SARS CoV-2 particles and distance: We have discussed in earlier reports that most new infections come from inhalation of the virus expelled by asymptomatic or pre-symptomatic people and that remains the case. Indeed, there may be a rather brief time interval in which infected folks are most contagious.[9]

We also discussed the range of particle sizes expelled in a cough or a sneeze - or an aria. Larger respiratory droplets tend to fall to the ground. The lighter the particle, the further in general it can travel. And with the sonication provided by rapidly vibrating vocal cords, the nasopharyngeal virus of an asymptomatic singer (or by the increased ejection velocity of a rapidly breathing exerciser, cougher, sneezer, or shouter) moderately sized particles of mucus water and virus can be ejected more than eight meters. The smallest particles - small enough for the evaporation of the water itself, can leave SARS CoV-2 suspended in the air for hours - though whether at an infectious dose would depend greatly on ventilation.[10] The mobility of such particles appears to be why the infamous Skagit County choir practice - of distanced singers - still resulted in so many infections.

It's as if any infectious person is in the center of a target with the heaviest virus-containing particles ejected with mere speaking falling in one concentric ring around them, then smaller particles in lesser abundance within other more distant rings (MOSTLY within about six feet) but even smaller particles projected further out until the very smallest can be caught up in air currents and not fall for hours. The infectious risk clearly drops with distancing. However, a six-foot distance provides risk reduction, not absolute protection from viral shots on goal.[11] The diameter of the target with a singer at its center will be significantly greater than for someone silent or talking softly.

Even six feet from a SARS-CoV-2 harboring patient (and safer for that empty box), you are. under the right circumstances, still vulnerable to violently expelled or airborne virus - like a goalie facing strikers from such a distance as to make a

successful kick difficult - but not impossible. The greater the distance the safer, but is there anything else besides distance - and avoiding the crowds of course that making distancing problematic?

Masks are NOT sieves. Spaces in the mask structure may be larger than the 100 nm diameter SARS CoV-2 and the mask still markedly reduces passage of the virus - the reference video is worth a thousand words. The previous update included the report of two Missouri hairdressers in close contact with 80+ clients while both were infectious. Like all their clients, masks were worn. No client contracted the virus even with the prolonged close contact of the salon. Universal masking (with surgical masks) is directly associated with reduced risks of infection in health care workers.[12] Taken together the implication is that while by no means absolutely protective, simple surgical masks reduce the risk of inadvertent spread of virus as well as of acquiring virus. (Homemade cloth masks are not likely as effective - see the video - though not yet studied).

So, goalies can further reduce the odds of a viral goal by the donning of a mask. Its impact on disease spread is most robust for the prevention of one's OWN spread of the virus. It's unfortunate that wearing them has been politicized - though I suspect nearly all would prefer that their surgeon be masked during their hip replacement to reduce the risk of wound infection. Commonly available masks handled properly cannot protect absolutely; but once again we are trying to tip the odds in our favor and there is no doubt about that impact. Of course, their value decreases as distancing increases.

HVAC: If going airborne is one way for the virus to evade the distancing/mask defense, another obvious defensive maneuver arises: ventilation. We discussed this in the last update but since then it has only become more clear - being outside where breeze can rapidly diffuse airborne virus and 'dilute it' to ineffectuality may reduce infection risk on the order of 20-fold.[13] Similarly many individual indoor infection events have been traced (especially in gyms or bars where loud voices and heavy breathing take place) to recirculated air and inadequate ventilation.[14] It seems increasingly likely that sub-optimal turnover and venting of room air contributes greatly to the indoor risk of contagion, suggesting that a substantial component of Defense is infrastructural - clearly a significant challenge.[15] And singing - like shouting - remains among the most efficient ways to eject virus into one's surroundings and therefore probably makes the role of ventilation particularly important. (Indeed, it is EXACTLY the unique challenge of singing with the exaggerated consonants, the sustained vocal cord vibration and the deliberate projection of sound and volume that makes it so difficult to confidently project the impact of interventions from other settings into a room of massed singers…)

Hand Washing: What else? The goalie can wash his or her hands frequently for the possibility that virus from a surface is transferred by hand to the nostrils. This has seemingly not been a big part of transmission but note from the WHO:

> "*Despite consistent evidence as to SARS-CoV-2 contamination of surfaces and the survival of the virus on certain surfaces, there are no specific reports which have directly demonstrated fomite transmission. People who come into contact with potentially infectious surfaces often also have close contact with the infectious person, making the distinction between respiratory droplet and fomite transmission difficult to discern. However, fomite transmission is considered a likely mode of transmission for SARS-CoV-2, given consistent findings about environmental contamination in the vicinity of infected cases and the fact that other coronaviruses and respiratory viruses can transmit this way."*[16]

Hence ongoing hand washing habits probably further reduce the chance of a viral score.

Spectrum of Risk: In short, the behavior of this virus and the Sabermetric approach to defending it suggests that our odds of avoiding infection are increasingly favorable as we take simple and logical steps to minimize shots on goal. The safest place to be is in the uncrowded outdoors. Handwashing is frequent and rigorous. As distancing is reduced, the value of masks rises. If indoors, the fewer people and the better the ventilation, the lower the risk. A Red-light/Green-light approach to integrating these risks and assessing activities and venues[17] is reproduced here and worth study. Note the 'shouting/ singing' categories….

Choral singing and Testing:

If a choral group could be assured that none of its members were contagious, the show would go on. Around the country the highly accurate Polymerase Chain Reaction-based tests, (PCR tests provided locally by the NM State Lab and TriCore and Qwest among others) have been often poorly available and too long in turnaround time to make this assessment. NM has had far better access AND turnaround time than most states, but 48-72 hours does not permit concert-day certainty of

singer health. But what if there was a simple self-administered rapid-result test that reliably provided concert- and practice-day assurance of NON-infectivity? The FDA has just approved such a test[18] and in academic studies of these kinds of tests - self-administered and saliva based - it appears that sensitivity and specificity of results are pretty good.[19] The predictive value of such tests is markedly affected by the prevalence of the disease in the community and false-positive tests (meaning drop-out of that person until the more accurate PCR test could confirm results) is on the order of only one in ten. False NEGATIVE results - that send an unwitting infected chorister to practice - is the bigger issue at one- to- two in ten in this meta-analysis. But it appears we may be closing in on the kinds of rapid reliable tests that could permit singing again - especially if distanced and outdoors or indoors with suitable ventilation as additional precautions. (Btw there are ceiling fan manufacturers now that have upward directed UV light on top of the motor and purport to drop airborne pathogens of all kinds by several orders of magnitude… see www.bigassfans.com) It may take several more months to know if this first glimmer of light holds up.

Choral singing and Vaccine

Another route to Choral singing is the assurance of immunity in all members through vaccines. The international alliance for vaccine development and distribution, COVAX, now reports the unprecedented cooperation of 172 countries involved in this work with,7 vaccines in trial form and another 9 in process.[20] These nearly all focus on that Spike Protein since if you can develop antibodies that recognizes and attach to it, you can potentially prevent it from 'fitting' into the ACE 2R receptor and gaining entrance to cells.

(Unfortunately, it does not seem that antibodies to other Coronaviruses 'cross over' to provide humeral immunity to COVID-19).

The NYTimes vaccine tracking site now counts 23 vaccines in Phase I trials, 14 in Phase II and 9 in Phase 3.[21] We discussed the phases of development in the last update but these are briefly reviewed at this useful site which lists each company involved as well. Notably two of the Phase III trials are for vaccines approved before the trials have been done - the Russian vaccine for instance. To Editorialize for a moment DON'T take a vaccine that has not demonstrated efficacy and safety in a PHASE III trial!

An inhaled virus blocks SARS-CoV-2 in mice[22] and efforts to create a human equivalent are underway[23] to take advantage of that IgA surface immunity discussed above. (And if you are wondering whether mice get COVID -19 the answer is no. Human ACE 2 Receptors had to be introduced into the mice to do those studies…)

Phase III trials are recruiting around the world but I don't believe safety and efficacy can be confidently evaluated before the end of this calendar year.

Contagion and Illness

Why is there such discrepancy in the severity of COVID-19? The simple answer is we don't yet know. The role of **co-morbidities** like Diabetes is well known but beyond the scope of this already tedious discussion. There seem to be differences in **individual immune responses** as well as small differences in **viral construction** that could play roles.[24] It has been noted too that in viral hot-spots where masks were used (even if distancing could not be implemented) disease severity was less for those who wore **masks** - suggesting that perhaps a larger initial dose of virus leads to more severe disease. Although the interest in a vaccine has us focused on the adaptive immune system and antibody production, there is also a cell-mediated "**Innate Immunity**" system in humans that may not get enough credit in COVID 19. There IS evidence that this system in some people had already recognized COVID-19 though they were never exposed[25] contributing to less severe disease. This in turn raises the possibility that exposure to those other Coronaviruses in the form of simple URIs (which did not induce antibodies) MIGHT nevertheless provide an accelerated immune response attenuating the illness…

Meanwhile with respect to contagion itself, we have previously discussed R_0 ("R-nought"), the Reproductive Number calculated for a contagious illness representing the average number of people infected by an index case. SARS CoV-2 appeared to have an R_0 of about 3 - accounting for the grave concerns amongst the Public Health community even before cases were known world-wide. Three infections each infecting three more means 9, 27, 81, 243, 729 and so on…. However, R_0 is an AVERAGE and we tend to think that means some people infect only 1 and others 4 or 5. But what if some infected 80 or 1000? Then that average R_0 of 3 (or a little lower) suggests that many people DON'T relay

the infection very effectively, while a smaller number of “super spreaders” do disproportionate dissemination.[26] I highly recommend that Vox article but have to say that to take advantage of the implications would require a lower prevalence of disease than we now have in most of the US, much more robust tracing infrastructure, substantially greater public acceptance of the process and an upgrade of CDC information systems. With respect to choral singing, these distinctions are probably not crucial.

At least two well documented cases of viral reinfection are now published. In one the second infection was more severe than the first but the immune response to the first had not been well documented.[27] We still don’t know the degree and durability of immunity conferred after infection in the vast majority of cases.[TA1]

[1] https://elifesciences.org/articles/57309

[2] https://elifesciences.org/articles/57309

[3] https://idpjournal.biomedcentral.com/articles/10.1186/s40249-020-00662-x

[4] https://www.sciencedirect.com/science/article/pii/S1573428505800079?via%3Dihub

[5] https://jvi.asm.org/content/79/23/14614

[6] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7245198/ and https://www.nature.com/articles/s41467-020-18058-8

[7] https://cvi.asm.org/content/23/6/438

[8] see http://med.stanford.edu/news/all-news/2020/08/immune-system-deviations-found-in-severe-covid-19-cases.html and https://www.nytimes.com/2020/06/03/health/coronavirus-blood-type-genetics.html

[9] See references cited in https://www.vox.com/21296067/coronavirus-covid-symptoms-superspreaders-superspreading-contagious-bars-restaurants

[10] https://www.bmj.com/content/370/bmj.m3223; and see van Doremalen N, Bushmaker T, Morris DH, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. *N Engl J Med*2020;382:1564-7. doi:10.1056/NEJMc2004973. pmid:32182409CrossRefPubMedGoogle Scholar

[11] https://www.bmj.com/content/370/bmj.m3223

[12] JAMA 8/18/2020 324:703 and there are many similar studies.

[13] Nishiura H, Oshitani H, Kobayashi T, et al. Closed environments facilitate secondary transmission of coronavirus disease 2019 (COVID-19). *medRxiv* 2020.02.28.20029272. doi:10.1101/2020.02.28.20029272Abstract/FREE Full TextGoogle Scholar - not yet peer reviewed

[14] See https://www.bmj.com/content/370/bmj.m3223 and references

[15] https://edlabor.house.gov/media/press-releases/gao-report-more-than-half-of-school-districts-need-significant-building-repairs-ventilation-systems-are-major-concern

[16] https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions

[17] from the BMJ article above

[18] https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-yale-school-public-health

[19] https://www.frontiersin.org/articles/10.3389/fmed.2020.00465/full

[20] https://homelandprepnews.com/stories/54572-covax-facility-gathers-172-countries-supporting-nine-covid-19-vaccine-candidates/

[21] https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html

[22] https://www.cell.com/cell/fulltext/S0092-8674(20)30742-X

[23] https://www.npr.org/sections/health-shots/2020/08/28/906797539/what-a-nasal-spray-vaccine-against-covid-19-might-do-even-better-than-a-shot

[24] https://science.sciencemag.org/content/early/2020/08/10/science.abc6261; https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31757-8/fulltext

[25] https://www.nature.com/articles/s41586-020-2550-z

[26] https://www.vox.com/21296067/coronavirus-covid-symptoms-superspreaders-superspreading-contagious-bars-restaurants

[27] See references in https://www.statnews.com/2020/08/28/covid-19-reinfection-implications/

[TA1]This is more about immunity than contagion, no?