Mathcamp Covid-19 Scientific Appendix

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Over the past two years, there has been an incredible effort in the scientific community to understand how SARS-CoV-2, the virus that causes Covid-19, evolves and spreads; the risk that Covid-19 poses to people of different ages and conditions; the efficacy of vaccines against infection and severe disease; the modes of transmission of the virus; and the best strategies to reduce its spread. In this document, we discuss key points from the scientific literature that inform Mathcamp's policies, providing evidence that:

- The risk of severe disease is low in young people, and extremely low after vaccination, coming within an order of magnitude of the risks from traffic accidents while driving to camp
- Vaccines continue to provide protection against severe disease even as the virus mutates and new variants emerge
- Rapid testing is an effective strategy to identify infectious cases early and prevent further spread
- Outdoor spaces, ventilation, masking, and limiting outside contacts provide additional powerful tools to reduce transmission

Pandemic Trajectory

The Covid-19 pandemic began in December 2019, as the SARS-CoV-2 virus, first detected in Wuhan, China, quickly spread around the world. Since then, scientists have learned an extraordinary amount about SARS-CoV-2 and the disease it causes, and developed a number of vaccines which are safe and highly effective at preventing severe disease. While the virus will continue to evolve (as all viruses do), producing new variants that circulate in new waves, some key features of the virus are likely to remain constant, allowing for sound planning and policy.

The precise shape of the long-term trajectory of the pandemic is difficult to predict, but we will eventually enter the endemic phase of the virus, in which it circulates at lower levels in the population. According to Dr. Yonatan Grad[1], "Enough people will gain immune protection from vaccination and from natural infection such that there will be less transmission and much less Covid-19-related hospitalization and death, even as the virus continues to circulate". As individual immunity wanes, infections will continuously recur, with occasional surges driven by seasonality, viral evolution (antigenic shift), and changes in human behavior patterns (Kissler[2]). Many scientists consider it likely that most people will be exposed to Covid-19 multiple times in their life, and that exposures beyond the first, once people have some prior immunity (due to vaccination, previous infection, or both), will tend to be more mild.

This pattern is familiar from seasonal influenza and from the four seasonal human coronaviruses that are among the causes of the common cold. All of these viruses recur periodically as children are born (providing new naive hosts) and as the virus mutates to evade prior immunity (antigenic shift). At least one, if not all, of the seasonal coronaviruses caused pandemics when human adults first caught them centuries or millennia ago. For example, the human coronavirus OC43 was likely responsible for the 1889-1890 pandemic (Vijgen[3] gives molecular clock evidence, Brussow[4] analyzes clinical symptoms), and now circulates in multiple variants, just as the Delta and Omicron variants of Covid-19 may continue to cocirculate. As in SARS-CoV-2, there are ongoing mutations in the spike protein of OC43, which may help it evade immunity generated in previous years and allow it to reinfect people during cold and flu season (Ren[5]).

We are currently watching this process of viral evolution happen in real time. While all viruses (and all living things!) mutate as they reproduce, the millions of coronavirus genomes deposited in public databases[6] allow the scientific community to see the interplay of mutation, selection, adaptation, and spread as it is happening.

The medium-term trajectory of the pandemic is hard to predict, including the timing of a peak, the depth of a trough, or when a new variant with different transmissibility, tissue tropism, or antigenic shift will emerge. But the current global testing and sequencing efforts do provide an early warning system for new variants, having given 1-2 month lead times before the Alpha, Delta, and Omicron surges in the US. This means that **an organization like Mathcamp can adjust its level of precautions strategically in response to impending levels of risk.**

Disease Risk and Vaccine Efficacy

Vaccination

Longitudinal studies show that vaccines provide significant protection against severe disease. A US study[7] found that two doses of the Pfizer vaccine remained 90% effective against hospitalization for at least six months, including against an emerging variant (Delta) with many mutations relative to the vaccine strain. Similar studies[8] in Qatar[9] and Israel[10] also showed no waning in protection against hospitalization for the Pfizer vaccine over ~6 months. The lack of data beyond six months is based on the time it takes to observe and study, but many scientists expect the protection to continue to last. At the time of writing, Omicron has become the dominant variant, and the large reduction in hospitalization rates for vaccinated individuals relative to unvaccinated individuals indicates continued vaccine effectiveness against Omicron.

Vaccines also play a role in reducing transmission, both by reducing the risk of infection in the first place and by allowing for a faster immune response to a new infection, resulting in a shorter infectious period[11].

The efficacy of a vaccine at preventing infection does wane with time, as the level of circulating antibodies decreases slowly after the body's last exposure to the virus. This is expected behavior[12], typical of the immune response to most infections; the immune system has to stand down eventually to reduce inflammation and prevent autoimmune disease. Memory B- and

T-cells persist, retaining the body's knowledge of the virus, and have the ability to rapidly reproduce to fight the virus when it is encountered again. According to Dr. Jennifer Gommerman[13], "Cellular immunity is what's going to protect you from disease…and vaccination [has] spurred durable cellular immunity. Circulating antibodies may be declining, but your immune system is capable of jumping into action once again."

This natural waning of front-line immunity, together with the occasional evolution of the virus to disguise itself from that immunity, means that reinfection becomes more likely with time. These factors allow for the seasonal waves of influenza and other coronaviruses, and the current wave of Omicron.

Severe Disease

The risk of severe disease caused by Covid-19 depends dramatically on age, with the risk of hospitalization approximately 160x higher for people aged 80-89 than for those aged 12-18 (Morris[14]). The prognosis for most young individuals with prior immunity (via vaccination or natural infection) who get infected is quite good. While some respiratory conditions are associated with a moderate increase in the risk of hospitalization from Covid, such as asthma (1.2x) and lung cancer (2.2x), these factors are far smaller than the protection afforded by relative youth and by prior immunity (Aveyard[15]).

Indeed, in the first year of the pandemic in the UK (March 2020-Feb 2021), before vaccines were available, Covid-19 caused only 25 deaths and 6,338 hospitalisations among the 12 million people under the age of 18. This is an absolute hospitalization rate of 1 in 2000 and a death rate of 2 per million, during a pre-vaccine period in which there was significant circulation (Ledford[39], Smith[16]). Covid-19 was rare as a cause of death, accounting for <1% of deaths in people under 18 in the study period. They estimate that there was one hospitalization per 100 cases, and 1 death per 20,000 cases.

Using the ~90% efficacy against severe disease (a 10x risk reduction) from the above section, we can approximate the risk to vaccinated children. (Note these data predate both the Omicron wave and widespread booster availability[1].) This back-of-the-envelope calculation yields a risk for vaccinated children of one hospitalization per 1000 cases and one death per 200,000 cases.

Comparison to Driving

To put these orders of magnitude into perspective, the US National Highway Traffic Safety Administration (NHTSA) has estimated that there are approximately 1.1 traffic fatalities in the

[1] A letter[17] in NEJM on Dec 29, 2021 from South Africa estimates that fully Pfizer-vaccinated but unboosted individuals maintain a 70% protection against hospitalization against Omicron. Given data[18] indicating that boosted individuals' antibodies are significantly more effective against Omicron unboosted individuals, boosters likely provide additional protection against hospitalization.

US per 100 million vehicle miles traveled and 55 people injured[2] per 100 million vehicle miles traveled (release[19], data). At this rate, the roundtrip drive from Boston Logan International Airport to Colby College of ~350 miles corresponds to a risk of fatality of 1 in ~260,000 and a risk of injury of 1 in 5200.

At the time of writing, during the Omicron wave in the US, there is some concern that both cases and hospitalisations are rising. It is important to note that the hospitalization data in the US does not separate people in the hospital *for* Covid-19 from those in the hospital *with* Covid-19, but admitted for another reason such as a surgery. For example, on January 4th, 70% of the hospitalized patients with Covid-19 in the UCSF hospital system in San Francisco were admitted for other reasons and were asymptomatic or minimally symptomatic (Graff[20]). The corresponding number in Los Angeles was ~66% (Money[21]). Even given this bias, ICU admissions continue to be far lower among vaccinated individuals (by a factor of 21.3 in Los Angeles county[22]). This makes a precise accounting of the risks associated with the current Omicron wave difficult to compute, and reaffirms the importance of vaccination.

Long Covid

In addition to the risks associated with the acute symptoms of Covid-19, some people experience longer-term symptoms[23] including chronic fatigue, post-exertional malaise, and loss of smell. Post-viral syndromes, perhaps mediated by some immune dysregulation, have been seen in other viruses, including SARS[24]. While early studies show that such “long Covid” outcomes are less prevalent[39] among vaccinated individuals[25] and among individuals with mild or moderate illness, these form a separate category of risk to severe acute symptoms and hospitalization. These risks provide an independent reason to mitigate the spread of Covid-19 even in cohorts who are quite unlikely to experience severe disease.

Transmission Dynamics and Prevention Strategies

It is now clear that Covid-19 transmission is largely airborne[26], and that there are sound strategies to prevent it. **A combination of outdoor spaces, ventilation, high-quality masks, physical distancing, and vaccines have been successfully used to significantly limit transmission** in workplaces (General Motors , NFL) and classrooms (LA Unified School District, Cornell University) around the world. Other interventions common earlier in the pandemic, such as frequent sanitization and plexiglass barriers, have proven ineffective and unnecessary.

Transmission Events

Most Covid-19 transmission occurs in indoor spaces where an infected individual shares air with others. The degree of infectiousness of an individual can vary vastly over the course of an infection, as two individuals who are both PCR positive may have viral loads differing by a factor

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[2] Here we multiply the 84 people injured by the 66% of them that are inside the vehicle. (The remaining 34% are motorcyclists, pedestrians, etc.)

of more than a million (Acharya [27]). Superspreading [28] events occur when a person with a high viral load encounters many people in an environment conducive to transmission. This means that preventing highly infectious individuals (who can be identified using rapid tests) from interacting with many people can significantly reduce the chance of an outbreak.

Because a significant amount of Covid-19 transmission is presymptomatic (usually in the 48 hours before individuals have symptoms), it is important to have prevalence-appropriate preventative measures in place to reduce transmission even when no individuals present appear to be sick.

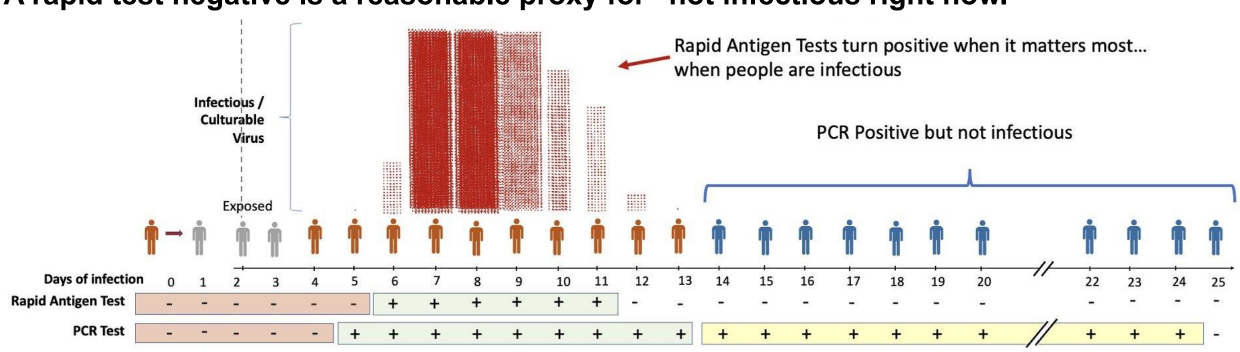
Testing

The two most widely available kinds of test for Covid-19 are:

- Laboratory PCR tests, which are highly sensitive but require shipping samples to a lab, with 1-7 day turnaround times.
- On-site rapid antigen tests, which are somewhat less sensitive and specific but return results within 15 minutes.

Dr. Michael Mina[29], among many others, has argued that frequent rapid tests[30] will offer greater sensitivity at a population level than infrequent PCR testing. Rapid tests capture the cases with the highest viral load, which are the most likely to be infectious. A study comparing PCR to the Abbot BinaxNOW™ rapid antigen test on Omicron cases from early January 2022 found that 95% of the PCR-positive specimens with high viral load (Ct < 30) were detected by the rapid test (Schrom[31]). In contrast, PCR tests may be positive for many weeks after symptoms have resolved and the individual is no longer infectious (as measured by the absence of cultural virus in their nose and throat).

A rapid test negative is a reasonable proxy for “not infectious right now.”



Slide by Michael Mina.

Careful modeling shows that rapid tests with slightly lower sensitivity can be more effective at preventing infections than more accurate tests with longer turnaround times. In one model[32] of screening before an event, a PCR test with a 24-hour turnaround time would catch 93% of people who would otherwise have shown up infectious, while a rapid antigen test administered at the event itself would catch 96% (see Figure 5 of Kissler[32]). Frequent testing with rapid tests offers a convenient way to identify and isolate a large percentage of infectious individuals.

Isolation

Isolation is the strategy of removing an infectious person from situations in which they might infect someone else. The duration of isolation is chosen based on the science of how the virus replicates in the body and how long people tend to be infectious. A Covid-19 infection proceeds through a period of exponential increase of virus in the first days, replicating in the airways and nose, followed by a few days of high viral load, in which the infected person is very infectious, followed by a longer fall off (Kissler[32]). There is significant variability in the exact timing of this process between individuals, with vaccinated individuals in general having shorter infectious periods and clearing the virus more quickly. Early quarantine and isolation durations were conservatively set to 14 days, and as more evidence has emerged about when peak infectiousness usually occurs, the CDC guidance has been lowered to 10 days and, in late December 2021, to 5 days for vaccinated individuals. These guidelines were meant to balance the prevention of infection against the disruption to daily life. Because of the high variability between individuals, it is useful to confirm the end of isolation with negative tests. That can allow them to safely return to regular activities sooner.

After someone has tested positive, it is important to identify close contacts who may have been infected. Because of the frequency of pre-symptomatic transmission, exposed individuals warrant additional monitoring (symptom checks and testing) and precautions. The extent of those additional precautions should depend on the prevailing conditions at the time.

A single Covid-19 case will not necessarily cause an outbreak. The probability that a close contact of an infected person contracts Covid-19 depends on the setting[33], varying from ~1% (work and school settings) to ~15-30% (shared households) (Winnipeg[34], Denmark[35] including Omicron). The appropriate response to an exposure will depend on the level of population immunity, the transmissibility of the current variant, the extent of precautions (including masking and ventilation). For example, many schools in the US have been using test-to-stay[36] procedures, in which asymptomatic close contacts are tested repeatedly, rather than being sent home to quarantine for 5-10 days. This has been as effective as quarantine at preventing cases among students, and represents a model which might be useful in a setting like Mathcamp as well. Where transmission has occurred, there is often additional transmission, so carefully following up on any cases to check for linked cases is important to catch potential outbreaks early.

Masks

Masks are effective at avoiding the spread of Covid-19 (by catching exhaled particles from an infected person) and at reducing the risk of contracting Covid-19 (by keeping particles exhaled by someone else out). While all masks offer some benefit, well-fitting[37] N95 or KN95/KF94 masks offer more protection[38] to the wearer than surgical masks and cloth masks.

Mathcamp as a Dynamical System

We conceptualize Mathcamp as a physical dynamical system with an interior (people at camp), an exterior (people outside of camp), and a boundary separating them. Covid-19 can enter camp by people crossing the boundary, as when campers, staff, or overnight visitors arrive, and by interactions at the boundary where a person at camp is exposed to a person outside camp, such as at the dining hall or gym. Once a person at camp is infected with Covid, the number of additional cases at camp generated will be a function of an effective rate of mixing inside the camp, determined by policies such as class density, social events, masking procedures, etc.

The total incidence of Covid-19 at camp will be a function of:

1. The rate of Covid-19 outside of camp
2. The rate of introductions across the boundary, of people coming into camp, modulated by precautions they take, including testing and masking
3. The rate of interactions on the boundary, modulated by the context and precautions taken, such as outdoor events and masking
4. The rate of mixing in the interior, at camp, modulated by context of internal camp activities

The basic philosophy being taken at Mathcamp this year is to take strong efforts to reduce the rates of transmission at and across the boundary (2 and 3) to allow for a higher rate of mixing in the interior (4) at a given level of overall risk.

The purpose of separate color-coded tiered systems for precautions at the boundary and within the interior is to allow for separate modulation depending on the level of Covid-19 outside and the risk of transmission occurring inside.

Federal, State, Local, and University Guidelines

State and local governments may issue binding public health orders; the host university may issue mandatory policies for people on campus; and federal agencies may issue guidelines. All of these will be integrated into Mathcamp's program, for purposes of compliance and safety.

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