

COVID-19 Information Summary 25 May 2020

This information comes mostly from the notes I have taken from TWiV. I will place my comments or explanations in red. I'm not a doctor, so take everything I write with a grain of salt. For most people, only the summary section will be useful, but I have included the rest in a PDF so that you can delve into more detail if you desire. In some cases, I will provide an expanded discussion or explanation of certain terms or concepts.

Summary

1. The CDC and several states have been combining PCR test data (test if you are infected now) and serology test data (test if you have generated antibodies--usually to a previous infection). This tends to make the data meaningless for anyone who is trying to understand infection rates, but it does inflate the test numbers and drives down the 'reported' positive rate. The virologists at TWiV were extremely critical of this, one calling it Lysenkoism, and another considering it a breach of the CDC charter. People who have been using the CDC's data for projections are unsure of the impact.
2. The Moderna mRNA vaccine has completed Phase I trials, per a press release (not a scientific paper). The trial was open label (not double blinded and not placebo controlled). It observed the generation of protective antibodies.
3. There is a warning not to take too much Vitamin D until it is completely studied. Do not take more than 4000 IU/day, unless a doctor recommends it. I had previously mentioned that low Vitamin D levels have been associated with worse COVID-19 disease outcomes and that many people self isolating or living at high latitudes will end up with low Vitamin D levels. So taking a Vitamin D supplement is fine, just don't go overboard.
4. There are several diagnostics tests that have had poor accuracy. Part of this may be due to the loosening of restrictions in order to boost test capacity. The tests TWiV had concerns with were from Quest and Abbot. In contrast, they praised Roche. For those getting diagnostic tests, realize that the accuracy of the tests is fairly flexible right now, and be aware of the impact of Bayes Theorem: <https://youtu.be/R13BD8qKeTg>
5. The USTA has issued guidelines on how to safely play tennis: <https://www.usta.com/en/home/stay-current/national/usta-statement-on-safety-of-playing-tennis-during-the-covid-19-v.html>
6. A Kawasaki-like illness has been observed in some children about 4-6 weeks after an infection. It is believed that it is an autoimmune disease caused by the antibodies generated combatting the initial infection. The symptoms are rashes, fever, abdominal pain, and strawberry tongue. It is unknown if it is acute or chronic.
7. Choirs may be at higher risk. A CDC MMWR report saw a high infection rate due to a choir practice in March. But this was before significant restrictions, such as social distancing or mask wearing, were in place.
8. The risk of illness is primarily due to aerosols or small droplets. The risk due to contaminated surfaces is lower. One virologist estimated the risks at 45% aerosols, 45%

small droplets, and 10% surfaces. It is also believed that smaller droplets can travel further into the respiratory system to cause a more severe disease.

<https://www.nytimes.com/2020/05/22/health/cdc-coronavirus-touching-surfaces.html>

Vaccines & Therapeutics

Convalescent plasma (contains IgG antibodies that previously sick individuals have generated).

- This is not serum, therefore it contains platelets and other elements that can cause clotting
- Not good to give late in the course of the disease due to potential thrombotic issues, as well as the fact that the virus tends to clear out before the most significant complications occur
 - Risk in 2nd & 3rd week of illness

ChAdOx vaccine

- “Chimp Adenovirus Oxford”
- Vectored vaccine that uses a plasmid (small piece of circular DNA) to encode the virus
 - Removed gene for a key protein required for the virus to replicate
 - It can only be grown in cells that are externally provided that protein
 - Added gene for the SARS-CoV-2 spike protein
 - An immunologist noted that there are huge differences between vectors used
- Previous ChAdOx created for MERS
- Currently chimera vaccines exist for Ebola (using VSV) and Dengue Fever (using Yellow Fever virus)
- Other viruses used for vectored vaccines
 - VSV
 - Pox viruses
 - Ad.5
- Repeated use issue
 - Immunity may be generated for vector, thus boosters will be rapidly cleared without generating a necessary immune response
 - Ex: repeated Botox may not work due to the rapid clearance by the immune system
- Combined Phase I&II trials
 - May be available as soon as May 2021
- Forbes article criticizing ChAdOx misrepresents data
 - A very high dose was given to the monkey, which is not necessarily representative of what a human would experience

Moderna Phase I mRNA Vaccine

- Press release, no paper
 - **Open label (not double blinded, not placebo controlled)**
 - Dose + booster
 - Lipid nanoparticle

- Uses pre-fusion form of SARS-CoV-2 spike protein
- Uses pseudo uridine vs uracil -> less innate immune response
- mRNA makes spike in cytoplasm
- Measured antibodies and neutralizing plaque assay
- **Seroconversion (generation of antibodies) observed**
- Also on clinicaltrials.gov
- Ph II & III complete as early as late fall
 - One virologist called this “borderline fantasyland”
- We don’t know correlates of protection, or the impact on CTLs (CD8+ T cells)

Potential problems with vaccines

- Antibody dependent enhancement (ADE)
 - Cat coronavirus (FIPV) & Dengue fever
 - Antibodies bind but don’t block
 - Allows virus entry into cells by Fc receptor
- Vaccine associated enhanced respiratory disease
 - RSV vaccine in the 60s
 - Still haven’t generated a RSV vax
- **Kawasaki-like illness**
 - **What if vaccine generates autoimmunity**

Remdesivir

- Dr. Griffin has not observed any exceptional changes (can’t tell if it is being used)
- Issued by FEMA based on specific criteria, which means it typically goes to very sick patients
 - It would be better to issue earlier, when the viral load is rising
- Requires IV

Vitamin D

- Need better data
- **Article warning not to take more than 4000 IU/day**
- <https://nutrition.bmj.com/content/early/2020/05/15/bmjnp-2020-000089>

SARS-CoV vaccines (original SARS of 2002-2003)

- Neutralizing immunity in animals
- Humans
 - Inactivated whole body vax -- 85% seroconversion in first dose, higher in second
 - Recombinant plasmid encoding spike vax
 - antibodies generated, but not neutralizing
 - CD4+ T cell response, small fraction (2/10) CD8+ T cell response
 - Cancelled investigations after SARS went away

Kawasaki-like illness

- Treated with combined pooled IV-IgG
 - Tells body it has done enough & shuts down production

BCG Tuberculosis vax

- Is there an impact on COVID-19?
 - 12 studies underway

- Commonly given in the past in Japan/Taiwan
- Vax has a transient effect -> why would it help older people?
- Test/Trace/Isolate is probably the cause of the reduced impact in Japan & Taiwan

Testing, Immunity, & Protection

Most robust immune responses -> worst outcomes

Poor diagnostics

- **Quest**
- **Abbot rapid PCR**
 - **Workflow has disrupted sensitivity**
 - **Real world sensitivity <50% (trash)**
- **Some tests leading to contradictory results**
 - **Simultaneous PCR (+) & IgG (+)**
 - **PCR (+) but later IgG (-)**
- **15 min PCRs**

Good diagnostics

- **Roche**

PPE works (Dr. Griffin still not infected)

Far UVC

- Bulbs very expensive \$500-\$1000
- Wrong bulbs can cause burns, blindness, melt plastic, etc.
- Far UVC doesn't penetrate skin or tear layer

PCR tests

- Ct (or Cq) varies based on the test

No gold standard tests out yet for comparison of sensitivity & specificity

Chest x-ray doesn't always detect ground glass pneumonia

- Need CAT scan

Herd immunity

- 70-80%

Immunity is not a binary term, there are shades of gray

Immunity discussion

- Gold standard for vaccines is sterilizing immunity
- Non-sterilizing will still reduce viral shedding
 - Ex: IPV (for polio) is not sterilizing
 - Common cold coronaviruses do not generate sterilizing immunity

SARS-CoV-2 Immunity

- Non human primates infected -> clear the virus -> reinfected later
 - Protected
 - Same result with DNA Vax
 - There was also a similar Chinese paper a while back with the same results
- No cross protection with cold CoVs

- But it may cross react with IgM tests

New PCR test

- Tests for common cold CoVs as well as SARS-CoV-2
 - 229E
 - OC43
 - HKU1
 - NL63

What is going on with saliva tests?

- Unknown

Tennis

- **USTA guidelines issued**
- <https://www.usta.com/en/home/stay-current/national/usta-statement-on-safety-of-playing-tennis-during-the-covid-19-v.html>

Symptoms & Disease Progression

Disease phases

- Pre-symptomatic
- Viral replication
- Cytokine storm (not all patients)
- Coagulation issues (not all patients)
- Late hyperinflammatory phase (not all patients)

Potential thrombotic issues (clotting inside of blood vessels)

- Pregnancy
- Hormonal therapy
- Contraceptives

Sneezing is not a symptom of COVID-19

Kawasaki-like illness

- Symptoms
 - **Rashes**
 - Smallpox-like
 - **Fever**
 - **Abdominal pain**
 - **Strawberry tongue**
 - Inflammation of blood vessels
 - Vasculitis
 - Septic shock
 - Hypotension
 - **4-6 weeks after initial infection**
- PCR negative
- “Late hyperinflammatory phase” (children), “small vessel vasculitis” (adults)
- **Probably autoimmune response, driven by production of IgG**

- **Don't know if acute or chronic**

Bacteremia similar to late stage flu

Loss of smell

- ~30-40%
- Milder cases
 - Some without any respiratory symptoms
- Probably due to infection in epithelial lining of nostrils

Very late symptoms

- Recurrent loss of smell & taste
- thick mucus
- Pain in joints of hands

Brain & CNS

- The neurological symptoms could just be cytokine responses
- No evidence
- In SARS-CoV-1 (original), there was RNA in cerebrospinal fluid (CSF)
- Human common cold CoVs
 - In CSF of Parkinson's patients
 - Child fatal encephalitis (rare)
 - Association, not causality
- Hard to figure out
 - Example: Enterovirus-68 paralyzes kids, but it was never found in CSF

Observations

Dental transmission

- High speed aerosols due to dental tools
 - Potential to bypass masks & N95s
 - Potential viremia with ultra-small particles (100 nm)

Permissive

- Heart, kidney, liver

Grows in salivary epithelium

Only 1 strain (media is confused)

Choirs at high risk

- **CDC MMWR report**

Kawasaki-like illness

- What will be the impact on summer camps & schools
- Previously we thought children were rarely affected

Only 10% of Ph I trials for medications end up beneficial

Some cases of PCR (+) 2 months out

- Is this just remnants or is viral replication still occurring

Molecular Cell paper

- Multibasic cleavage site necessary for infection in human lung cells

- Furin cleavage site in spike
 - Not in SARS-CoV-1
 - Not in RaTG13
 - 2/4 cold CoVs have site
 - MERS has site
 - Newly discovered virus RmYN02 (closest relative) has spike
 - Hunan province (about 1000 km away from Wuhan)
- Other protease is TMPRSS2

Antibody surveys

- Spain ~5%
 - Implies IFR ~1.2-1.4%
- Italy ~5%
- Sweden ~5%
- Denmark/Norway ~1%
- Previous high number surveys may have selection biases (people who were sick volunteer to get tested)

Christian Drosten back of envelope calculations

- 45% risk is aerosols
- 45% risk is small droplets
- Only 10% risk is fomites
- Similar CDC guidance
 - <https://www.nytimes.com/2020/05/22/health/cdc-coronavirus-touching-surfaces.html>

Cigarette smoke

- Increases ACE2 receptors in respiratory tissue
 - Still can't conclude smoking affects the disease by this method (there might already be enough ACE2 receptors that there isn't a bottleneck)

Stanford physician scientist Ioannidis

- Heavy criticism

Assay virus requires BSL-3

Treatment trials in New York shutting down due to lack of patients

- Expect resurgence in fall and winter

Patterson, NJ has done a good job of contact tracing

There is a skew of 2:1 male:female

Press releases by drug companies

- Required for shareholder information
- Full release risks ability of scientist to present data at conferences
- SEC regulations to prevent insider trading

DHS decay of SARS-CoV-2 website calculator

- Laboratory conditions
- <https://www.dhs.gov/science-and-technology/sars-calculator>

News

Mumbai lockdown

- 20M people, high density
- 8 people/room, high temp
 - People will go out into streets no matter what

Ecohealth Alliance Grant cancellation

- **Surveys coronaviruses in bat populations in China**
 - **Critical for virological research**
- Purely political

CDC combining PCR & Serology data

- **Also occurred in Texas, Florida, Pennsylvania, Georgia, Vermont, Virginia, and Maine**
- **Makes data meaningless, and makes it impossible to know what is going on**
- **Inflates test numbers and drives down positive rate**
- **Criticism**
 - **Lysenkoism**
 - **A breach of the CDC charter**
- **Could impact projections**