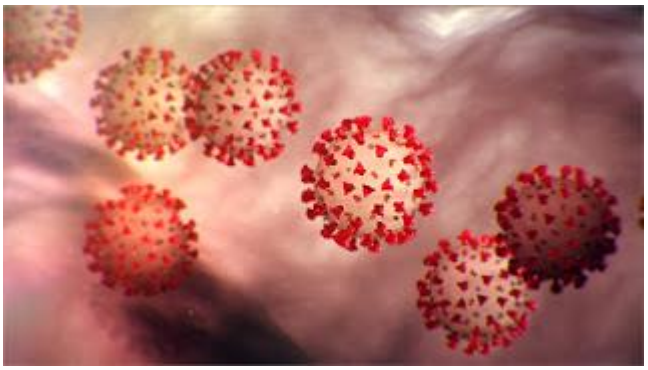


COVID-19 VACCINE: AN UPDATE AND PRIMER

ABSTRACT
This Note is an update examining the current vaccine approaches for the COVID-19 pandemic. It also provides an update and detailed analysis of the pandemic and its progression. Specifically we show that the current wave has some dramatically different characteristics of the first wave, namely a drastically lower death rate, 0.5% versus the earlier one of 10% in New Jersey. Demographic analysis also shows clusters and are suggestive ore more accurate and precise remediation.

TERRENCE MCGARTY

TGL 180, NOVEMBER 2020

Notice

This document represents the personal opinion of the author and is not meant to be in any way the offering of medical advice or otherwise. It represents solely an analysis by the author of certain data which is generally available. The author furthermore makes no representations that the data available in the referenced papers is free from error. The Author also does not represent in any manner or fashion that the documents and information contained herein can be used other than for expressing the opinions of the Author. Any use made and actions resulting directly or otherwise from any of the documents, information, analyses, or data or otherwise is the sole responsibility of the user and The Author expressly takes no liability for any direct or indirect losses, harm, damage or otherwise resulting from the use or reliance upon any of the Author's opinions as herein expressed. There is no representation by The Author, express or otherwise, that the materials contained herein are investment advice, business advice, legal advice, medical advice or in any way should be relied upon by anyone for any purpose. The Author does not provide any financial, investment, medical, legal or similar advice in this document or in its publications on any related Internet sites.

Furthermore, this document contains references to and quotes from papers and documents under the premise of Fair Use in order to present ideas and understandings in context. The Author has attempted to make any and all references to such material separate from those of the author per se and has referenced the source expressly in all cases. These documents are for the dissemination of ideas and have no commercial intent. The Author would appreciate any communications relating to these documents and these should be sent to:

tmcgarty@telmarc.com.

Contents

1 Introduction 5
2 Some Statistics 9
2.1 Incidence and Prevalence 9
2.2 Death Rates and Deaths 17
2.3 Doubling Time 20
2.4 Some Demographics 21
2.5 Testing 27
3 Viral Basics 30
3.1 Families and Genus 30
3.2 Infection 30
3.3 Corona Specifics 31
4 Immune System Basis 36
4.1 Antigens 36
4.2 Antibodies 36
4.3 Antigen Presenting Cells 37
4.4 B and T Cells 39
5 Vaccine Options 44
5.1 Virus Based 44
5.2 DNA Vectors 45
5.3 RNA Vector 45
5.4 Protein Vectors 46
5.5 Viral Vector 47
5.6 Recent Status 48
6 mRNA Vaccine Details 51
6.1 Principles 51
6.2 Production 53

6.3 Execution 56
7 Observations 58
7.1 Poly-specific Nanobodies 58
7.2 Masks vs no Masks 58
7.3 Immunization Strategies 60
7.4 Herd Immunity 61
7.5 Politics 61
7.6 Execution 63
7.7 Experts vs Amateurs 65
7.8 Useless Models 68
7.9 Schools, Vaccines, and the Virus 69
7.9.1 Facts 69
7.9.2 Proposal for Risk Mitigation 70
7.9.3 Protection of the teacher. 70
7.9.4 Protection of the Student. 71
8 References 73
9 Index 79

1 INTRODUCTION

We thought it would be worth a brief review of the current status of the COVID vaccine process. As with everything else with this disease it is a moving target so what we say today can readily be changed tomorrow.

We first begin with some detailed statistics from New Jersey. On February 4, 2020 we had noted that this would be a pandemic[1]. Since then we have been following and writing on the progress of this virus. Regrettably it has become a massive political football with more disinformation rather than facts. Thus, our attempt herein is first to examine the "facts" as are available. We have been tracking them daily along with the thousands of papers being written on the topic. The key observation of the facts in New Jersey are multifold:

1. A second flare up is occurring. This is most likely a result of the opening of schools as well as large social gatherings. There is no news there of course. Reasonable protection works, unreasonable actions spread the virus.

2. The mortality rate has dropped from 10% to 0.5%. Mortality is still dominated by pre-existing conditions but with only a 0.5% rate for those generally healthy it is not a Black Plague event by any means. The high death rates early on were the result of the State knowingly sending infected patients to nursing homes where unprotected residents died like flies.

3. There is a significant ethnic difference. We demonstrate that economic status seems irrelevant but that Hispanics are hit harder than other ethnic groups. One can speculate but it is just that, speculation. In fact, Hispanics are infected at twice the rate of any others. Moreover the peak infection age is 20-35.

4. Testing is highly problematic. Testing is still difficult to get. The sites have been closed down in the State and the results are often delayed days if not weeks. This has never been remedied and thus the tracking data is highly suspect. It is all we have however.

5. Data is extremely noisy and thus is a poor metric for tracking. Delays, inaccuracies, errors, are rampant. Misdiagnosis is a common issue thus distorting the results.

From the recent paper by Maurens and Fauci they list somewhat generally some of the more significant past plagues/pandemics have looked like.

[1] http://terrymcgarty.blogspot.com/2020/02/coronavirus-some-thoughts.html

Year	Name	Deaths	Comments
430 BCE	‘‘Plague of Athens’’	100,000	First identified trans-regional pandemic
541	Justinian plague (Yersinia pestis)	30–50 million	Pandemic killed half of world population
1340s	‘‘Black Death’’ (Yersinia pestis)	50 million	Pandemic killed at least a quarter of world population
1494	Syphilis (Treponema pallidum)	>50,000	Pandemic brought to Europe from the Americas
c. 1500	Tuberculosis	High millions	Ancient disease became pandemic in Middle Ages
1520	Hueyzahuatl (Variola major)	3.5 million	Pandemic brought to New World by Europeans
1793–1798	‘‘The American plague’’	25,000	Yellow fever terrorized colonial America
1832	2nd cholera pandemic (Paris)	18,402	Spread from India to Europe/Western Hemisphere
1918	‘‘Spanish’’ influenza	50 million	Led to additional pandemics in 1957, 1968, 2009
1976–2020	Ebola 15,258 First recognized in 1976		29 regional epidemics to 2020
1981	Acute hemorrhagic conjunctivitis	rare deaths	First recognized in 1969 pandemic in 1981
1981	HIV/AIDS	37 million	First recognized 1981 ongoing pandemic
2002	SARS	813	Near-pandemic
2009	H1N1 ‘‘swine flu’’	284,000	5th influenza pandemic of century
2014	Chikungunya	uncommon	Pandemic, mosquito-borne
2015	Zika	1,000?	Pandemic, mosquito-borne

Unfortunately many of these past have drastically different means of spread. Take the Black Plague of 1348. It was a disease vector from a flea on a rat to humans. If one wore clean clothes, slept in clean quarters and bathed, uncommon at the time, one had little if any risk of infection. TB and STDs also had a somewhat controlled transmission path. COVID-19 is different in that its transmission is person to person most likely via aerosols. The actual complete transmission paths are still open questions. In fact much of COVID-19 can fall in the category of "we don't know".

On February 4, 2020 we wrote about what we called the Corona Pandemic:

Infection by a virus like coronavirus is often through the nasal passages or the eye. At time it may be inhaled via the mouth or transferred via food.

However, if one looks at the masked Chinese one sees glove-less hands and cell phones. The cell phone is the petri dish for corona. The device is swung about, exposed to everything, holds virions, transfers them to hands and from there to eyes. The mask at best prevents expelling outwards. The eyes are unprotected but they are great sites for internal infection.

When in a potentially infectious site, we would focus first on eyes, then hands, then nose, then mouth, then whatever else can be covered. But when looking at pictures from China the eyes and hands are all exposed and most are carrying cell phones. They become walking transmitters of the virus.

Needless to say few were listening at that time. On February 25, 2020 we wrote:

The CDC is allegedly tracking and mitigating the Corona virus. One need look no further than their web page to note:

CDC is closely monitoring an outbreak of respiratory illness caused by a novel (new) coronavirus. The outbreak first started in Wuhan, China, but cases have been identified in a growing number of other international locations, including the United States. This page will be updated regularly on Mondays, Wednesdays, and Fridays.

OVID-19: Confirmed Cases in the United States

Travel-related: 12
Person-to-person spread: 2
Total confirmed cases: 14
Total tested: 426

Yes, they have tested only 426 as of today. One would think that testing would be in the tens of thousands just to get baseline samples epidemiologically. But after all it is our Government. we guess we have to wait for the television documentary on another Government failure. And you want these folks to manage all your health care! As StatNews relates:

The CDC urged American businesses and families to start preparing for the possibility of a bigger outbreak. Messonier said that parents should ask their children's schools about plans for closures. Businesses should consider whether they can offer tele-commuting options to their employees, while hospitals might need to look into expanding telehealth services, she said. "Disruption to everyday life might be severe,"

Messonier said, adding that she talked to her children about the issue Tuesday morning. "While we didn't think they were at risk right now, we as a family ought to be preparing for significant disruption to our lives." Messonier said the CDC is in conversation about whether to change the case definition that triggers a sick patient to be tested for the virus. Currently, health officials recommend testing only for people who have respiratory symptoms and have recently traveled to China, or those who have been in close contact with someone who was infected. But as community spread picks up in other countries, the case definition could change.

A warning is nice but how about massive distribution of testing kits. Perhaps education, warnings, but then again, the trust in the Government has deteriorated so badly that it is not clear that anyone would believe them. One wonders how long before this becomes a massive political football.

Again, few were listening. On march 9, 2020 we had meetings in New York, one at New York Presbyterian downtown on Worth Street. It was clear at the time that a pandemic was on the way but there were few if any precautions.

In this report we focus on the mRNA vaccines which are being produced. Clearly there are other options which will also comment on. However, the mRNA vaccine is an attractive alternate since it can more easily enter a cell, namely it folds easily, and it can be produced more readily, and is scalable.

2 SOME STATISTICS

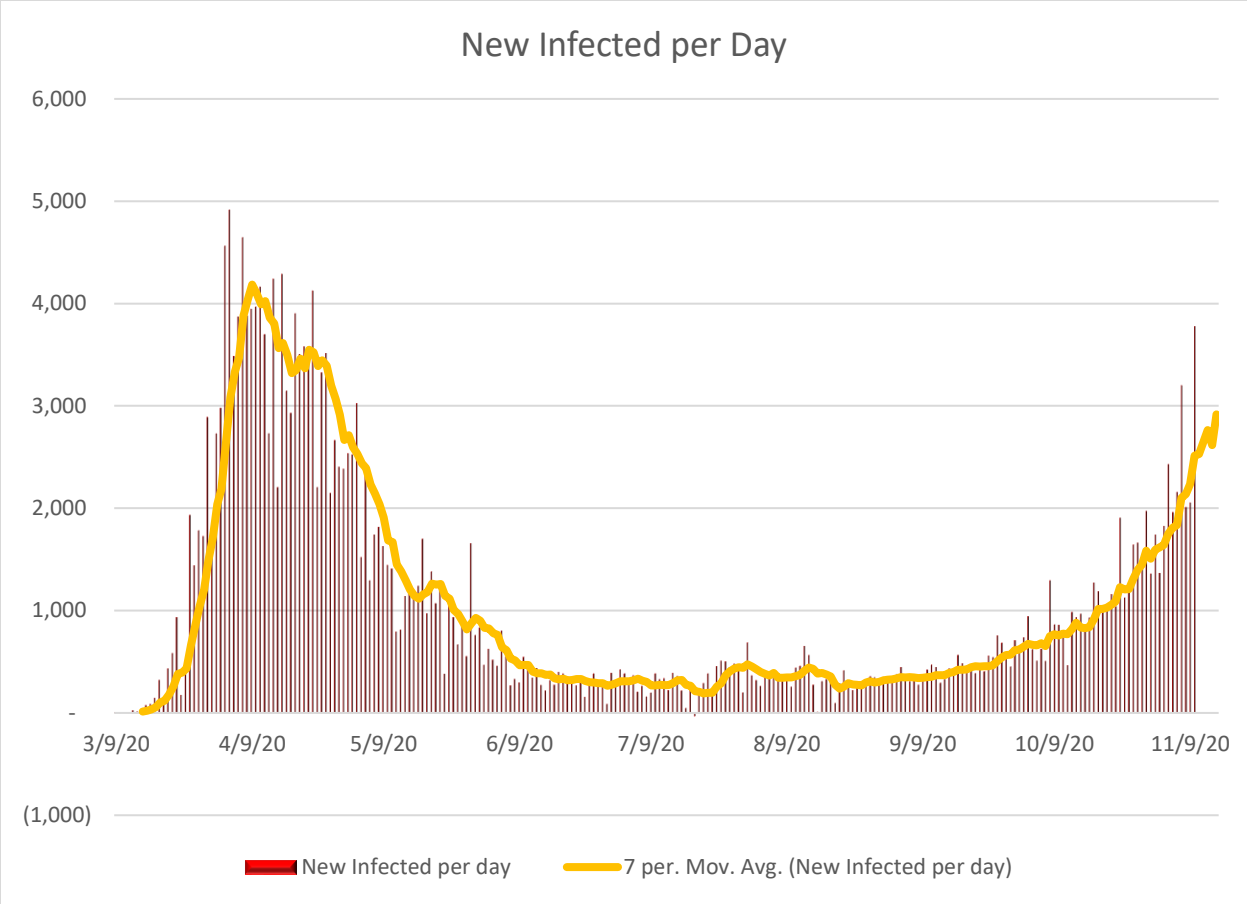
We have been following this pandemic since late January of this year. We have particularly focused on New Jersey since that is where we live and where the pandemic first exploded. It also has the best set of statistics since we have been watching and recording daily since the State started listing data. Our focus has been on incidence, prevalence and deaths. Examining the data on a daily basis gives one a deep understanding of the dynamics of this virus.

Unlike the Black Plague of 1348 which killed some 20 million, a third of the population and infected more than half of the population, and did so in two years or less, we in the US have had some 10 million people infected out of 330 million and 220,000 deaths. The death rate at the beginning was in excess of 8% and now is less than 0.5%. Much of that change is the loss of tens of thousands of long-term care residents who were exposed deliberately to the virus by Government mandate. But that will be a story for another date. Thus, statistically, thus far, this is not the Black Plague nor is it even the 1918 flu. The data does tell a story but regrettably it appears that politics has become an integral part of the tale as well.

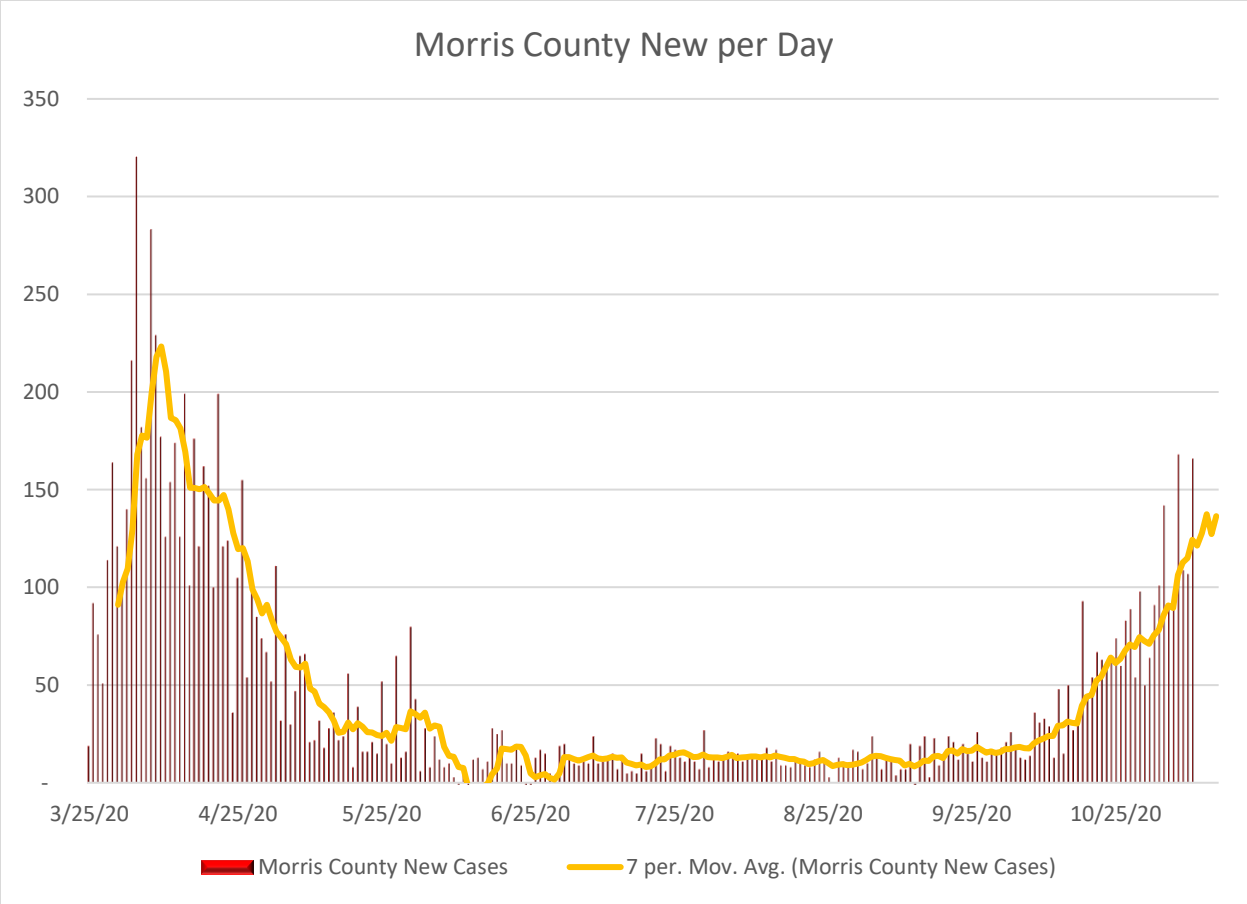
2.1 INCIDENCE AND PREVALENCE

Let us start with incidence and prevalence. The data shown has been collected from the New Jersey site. As one looks at the data one must understand that it is highly noisy and corrupted. Number change and dates do not reflect actual dates. Thus it is a noisy data set but useful.

First, we examine daily incidence. We started collecting data the first week in March. The results for the State wide are shown below.

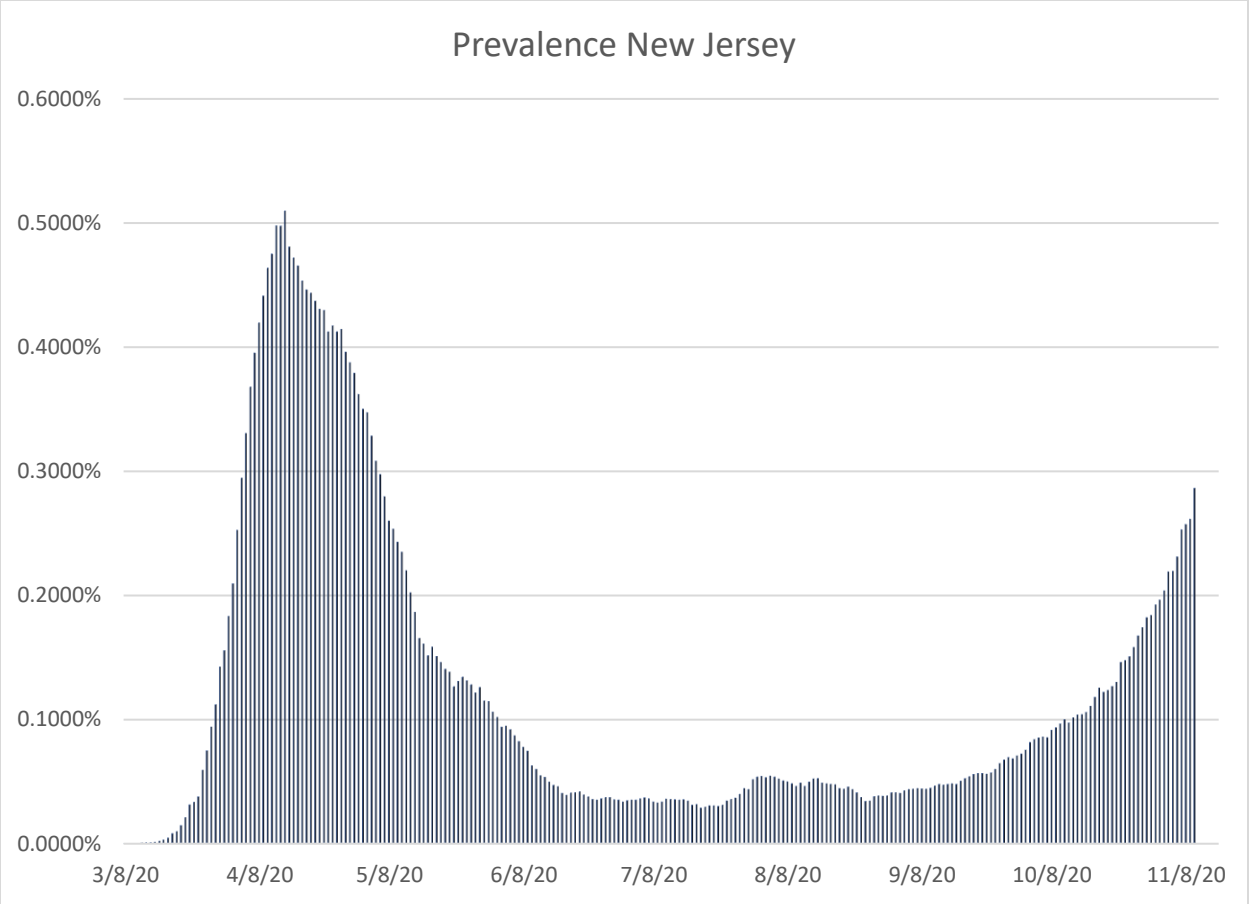


In a similar manner the daily incidence results for Morris County appear below.

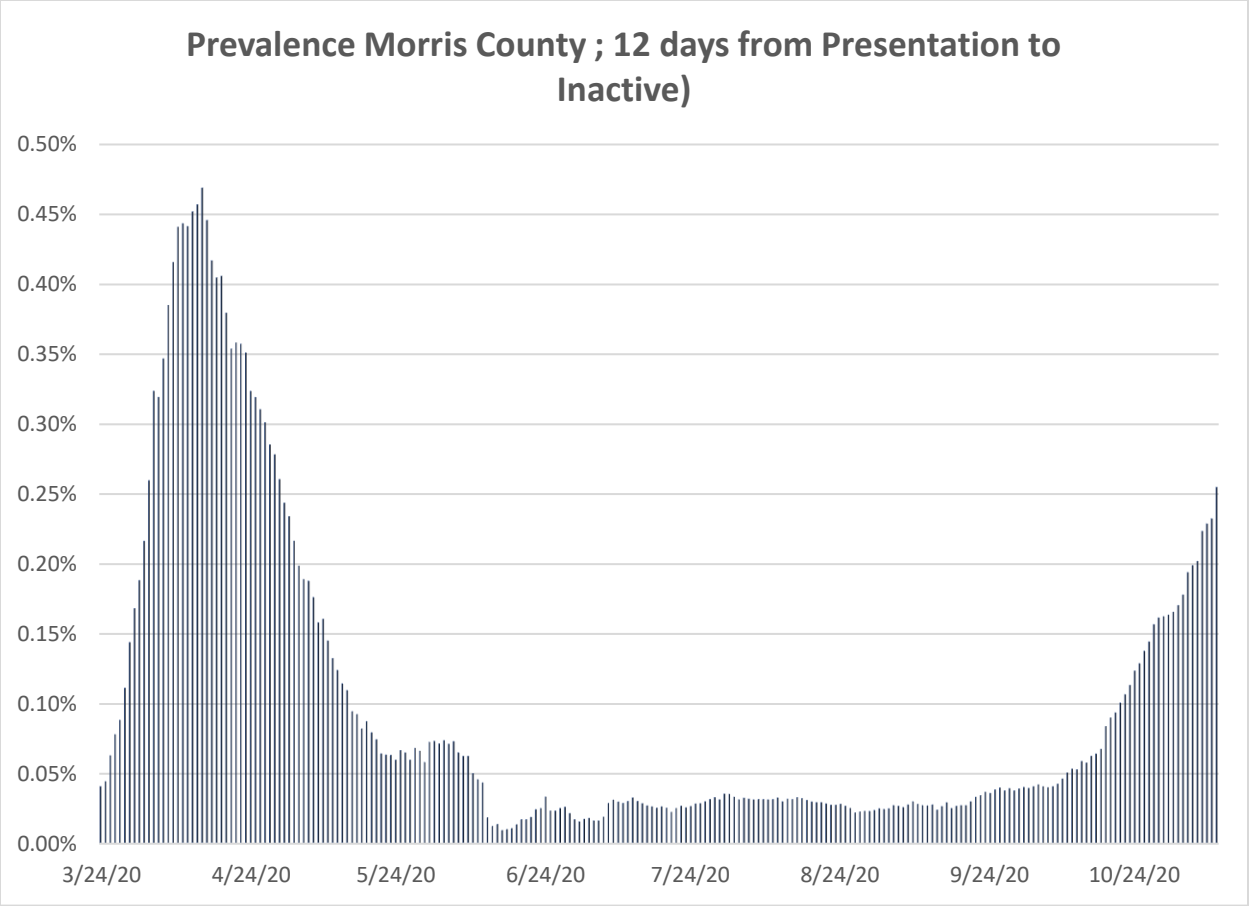


Both County and State are comparable, namely the first peak and the newer peak. We suspect the second peak is the result of a combination of school reopening and resultant young school age infections and then the spreading via large social gatherings. We have observed large gathering of youth after school recess as well as school managed sports events with massive crowding on basketball courts and the like. We have observed via the data that infections recognized by testing is low in the under 17-year-old group. Most likely the infections are quite high but indolent. Yet they are spreaders to older persons. Regrettably the State Health Departments seem to have failed to grasp this issue. It does demand field observations as well as mandatory weekly testing as we have argued for consistently.

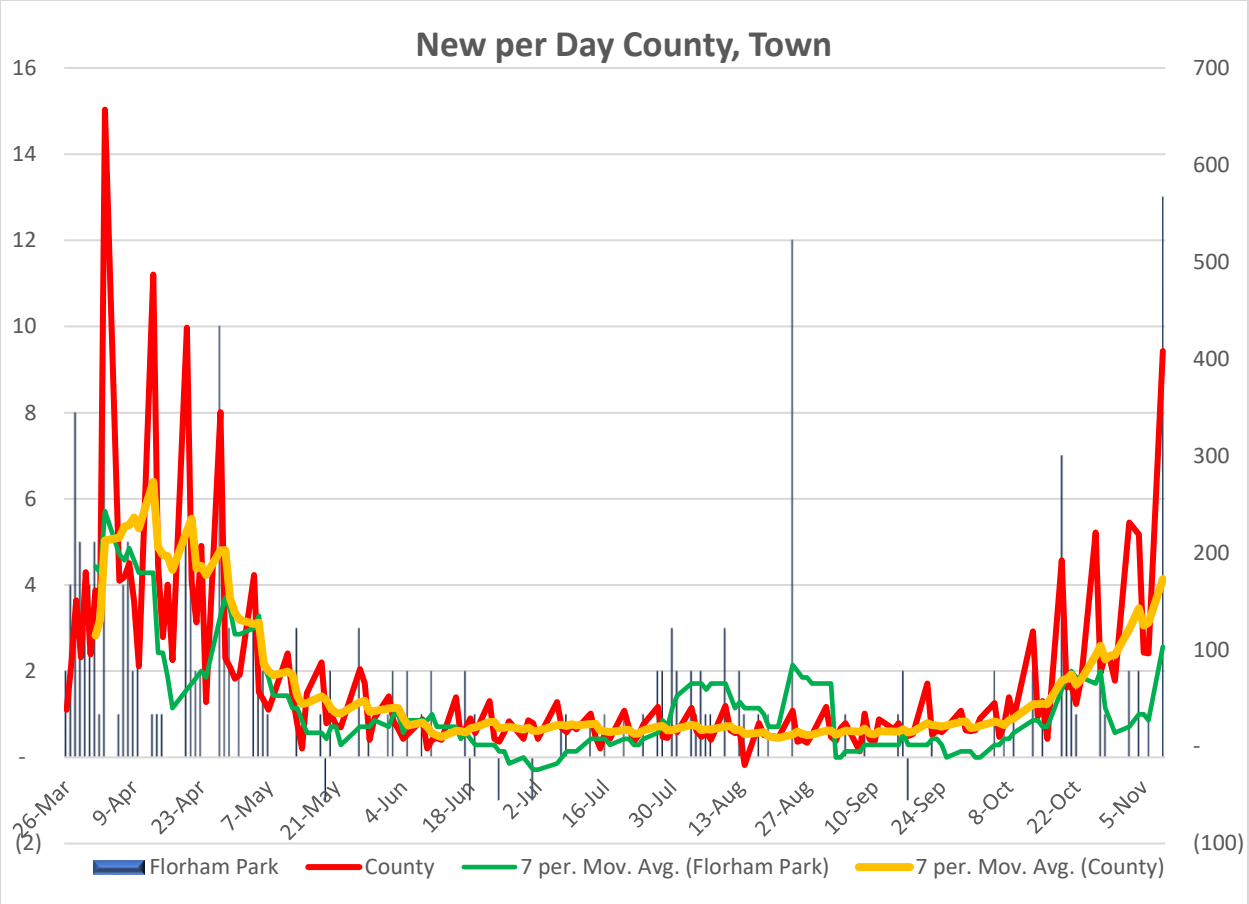
We now show the Prevalence for the State and County as follows. We assume that a person is contagious for twelve days after being tested and positive. In actuality the data on a daily basis does not reflect when the test was done nor does it reflect when it was reported. Furthermore, the data does not reflect the state of infection when the test was performed. Namely the data is highly noisy and substantially delayed. Thus, it may be something akin to 24-30 days after infection. As a note this is why Contact Tracing is useless in tracking this pandemic.



The County Prevalence data is shown below. It also shows similar trends. Note that we have a prevalence of an infected person being 0.25%. Basically 1 in 400 people are carriers in the County. This compares to 1 in 300 for the State. Since this lacks the untested carriers we wonder how this could be increased. Without data, it is impossible and the State seems to refuse to take this step. But even at that if only 1 of 400 have the virus as a carrier one can assess risk. Since it takes close proximity and a somewhat prolonged exposure, then the risk for those not deliberately exposing themselves to such a condition is miniscule.

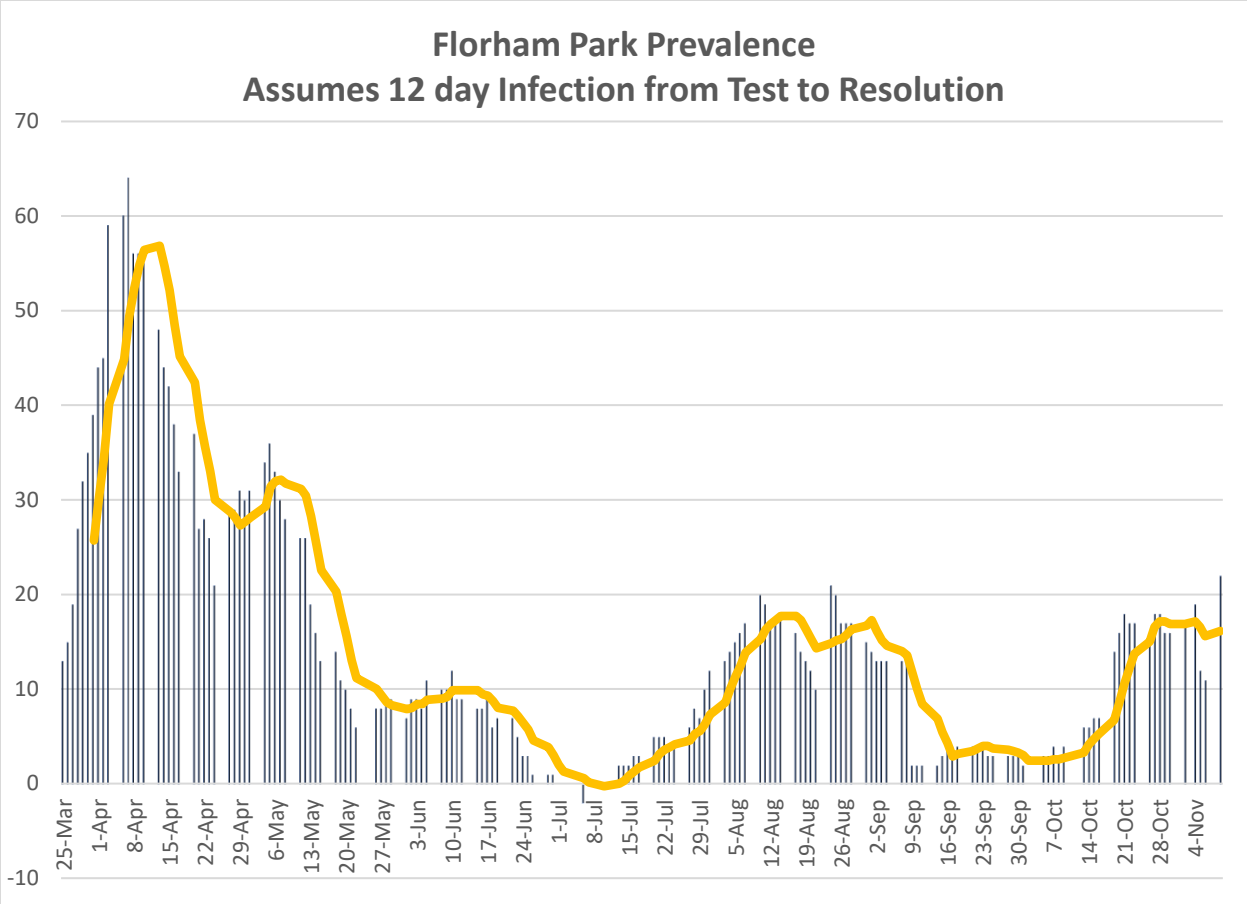


Finally below we show the County and Town data incidence as reported. What is often surprising is the large spikes, always on a Monday, reflective of delayed reporting and not a single day outbreak. Again one cannot really use the raw data as is.



Finally, we provide the Town prevalence. It is interesting to see the somewhat cyclical data and seeing that we now have peaks of 20 infected out of a population of about 12,000[2].

[2] https://en.wikipedia.org/wiki/Florham_Park,_New_Jersey



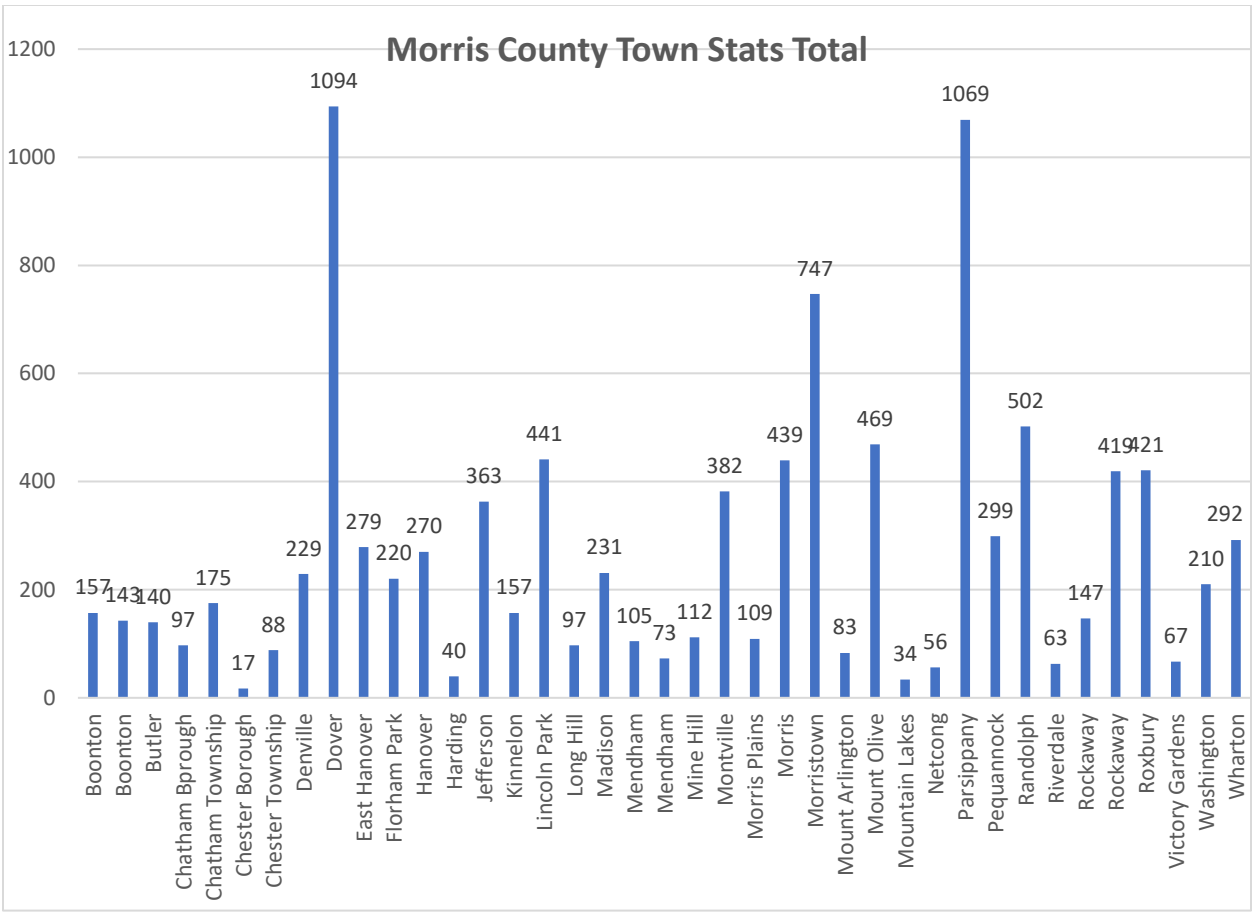
The above has certain characteristics:

1. There is a periodicity in the short term due to the nature of reporting. No data is reported on weekends and thus Monday peaks.

2. There is a periodicity in the long term for reasons we do not fully understand.

3. There is spiking due to certain holiday gatherings, the most recent the Halloween parties and gatherings, especially Hispanic Day of the Dead.

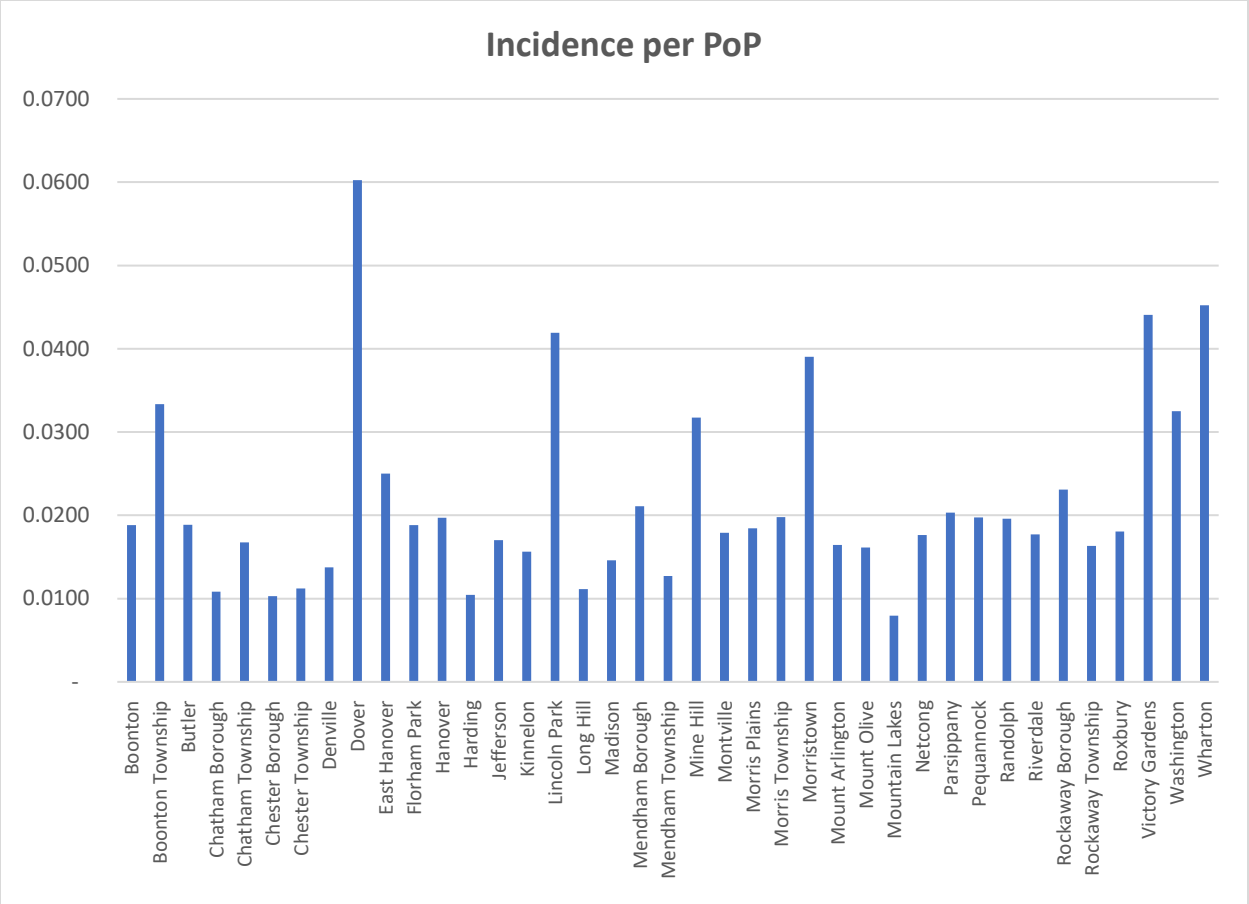
Now if we examine the individual town levels we obtain the data as shown below. This demonstrates dramatic peaks in certain towns. It is somewhat reflective of population however it is more reflective of demographics and housing density. Namely there are larger Hispanic populations and more high density residences.



In the above the two towns of Dover and Parsippany dominate the results. This has become more apparent as time has gone by. Dover has a population of 18,000[3], 50% more than Florham Park. But its infections have been five times higher. Parsippany has a population of about 50,000[4] which is about four times that of Florham Park. Yet it also has an infection rate of five times. Thus, Parsippany is somewhat comparable to the other towns whereas Dove is a substantial outlier. Also Dover has a Hispanic population in excess of 60% unlike Florham Park and Parsippany.

[3] https://en.wikipedia.org/wiki/Dover,_New_Jersey

[4] https://en.wikipedia.org/wiki/Parsippany-Troy_Hills,_New_Jersey

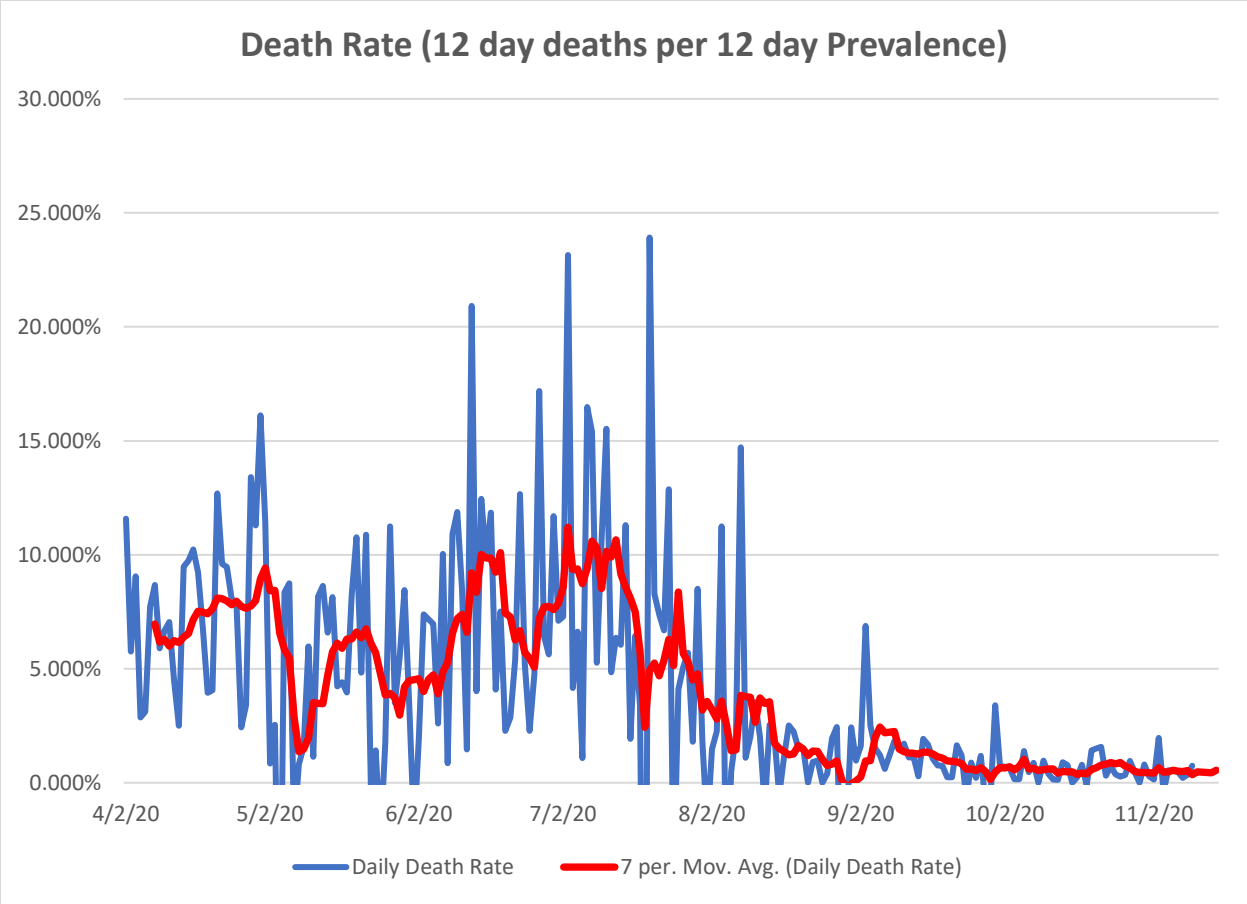


The fundamental conclusion from this ongoing analysis is that there are young spreaders and the towns are well demarcated. Thus a scalpel and not a hatchet should be the strategy. Now immunization will be a complex issue here as we shall see.

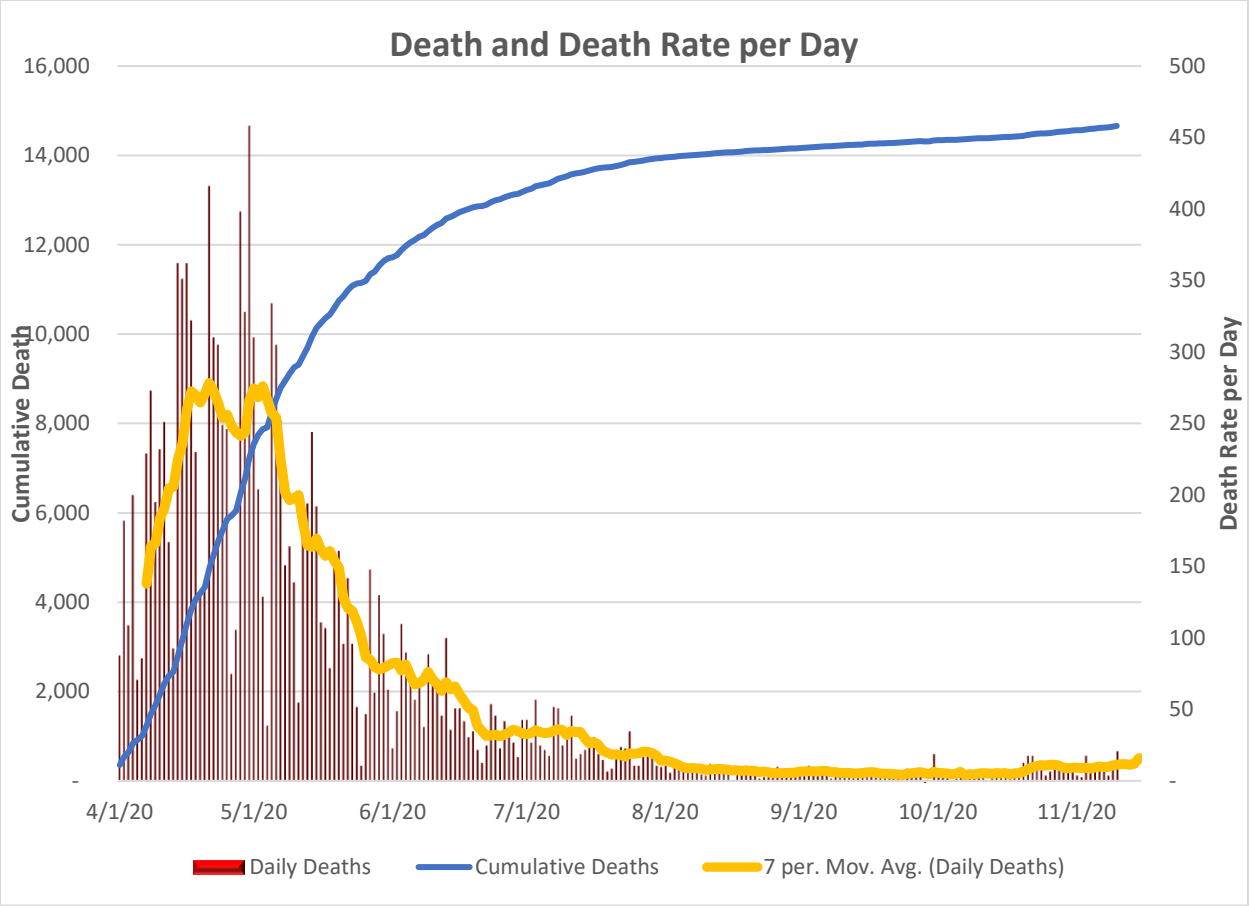
2.2 Death Rates and Deaths

We can now consider the death rates. We determined this using a 12 day death window with a twelve day prevalence. The result is shown below. Note the high mortality in the first phase. The rate was near 10%. The noisy data again is less reflective of fact than of how the data was collected. We generally focus on a seven day moving average.

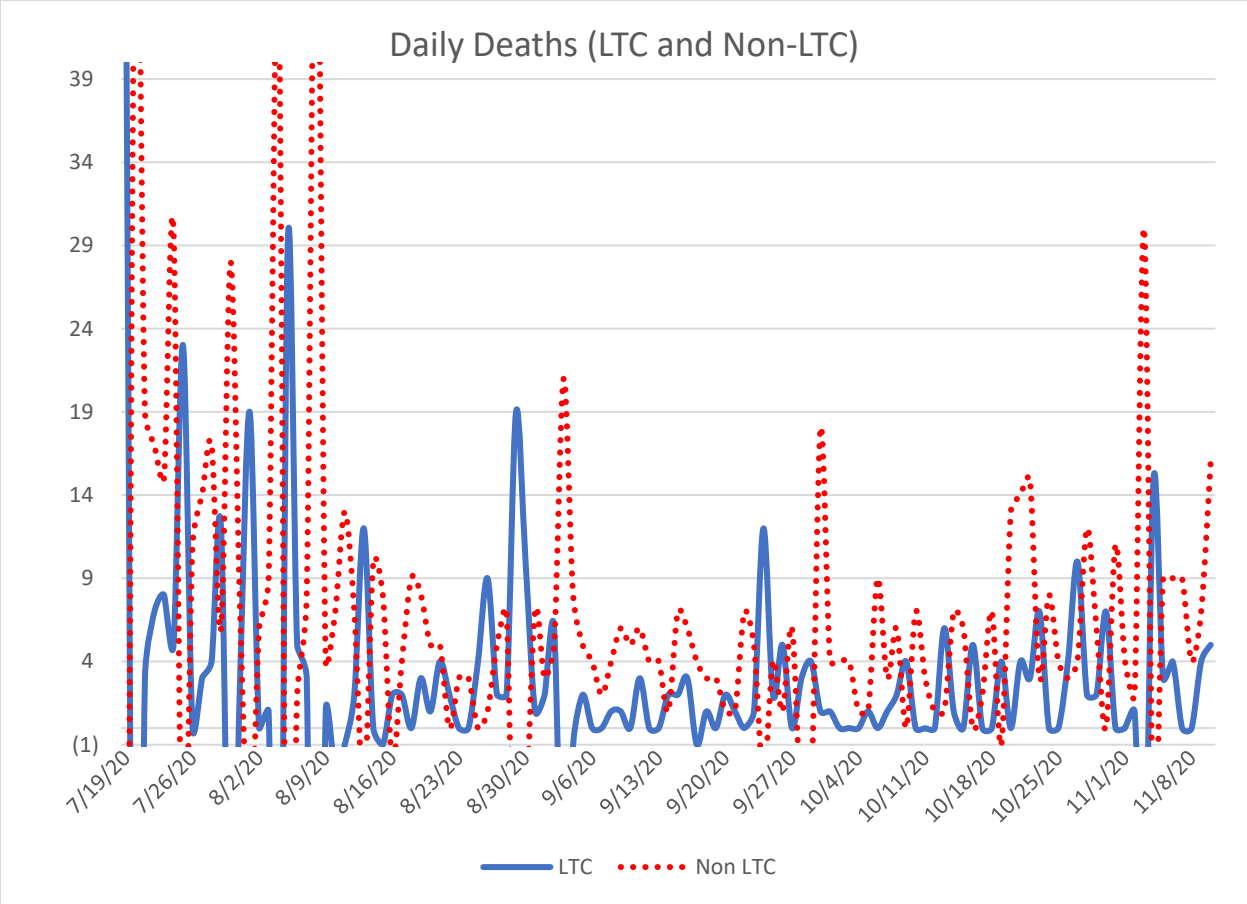
Now the death rate is down to 0.5%. That is a twentyfold decrease in mortality. We suspect it is a result of the high LTC deaths early on as well as those with significant co-morbidities.



The Figure below is the daily tally and the cumulative. We see a rising curve due to the substantial increase in infected.



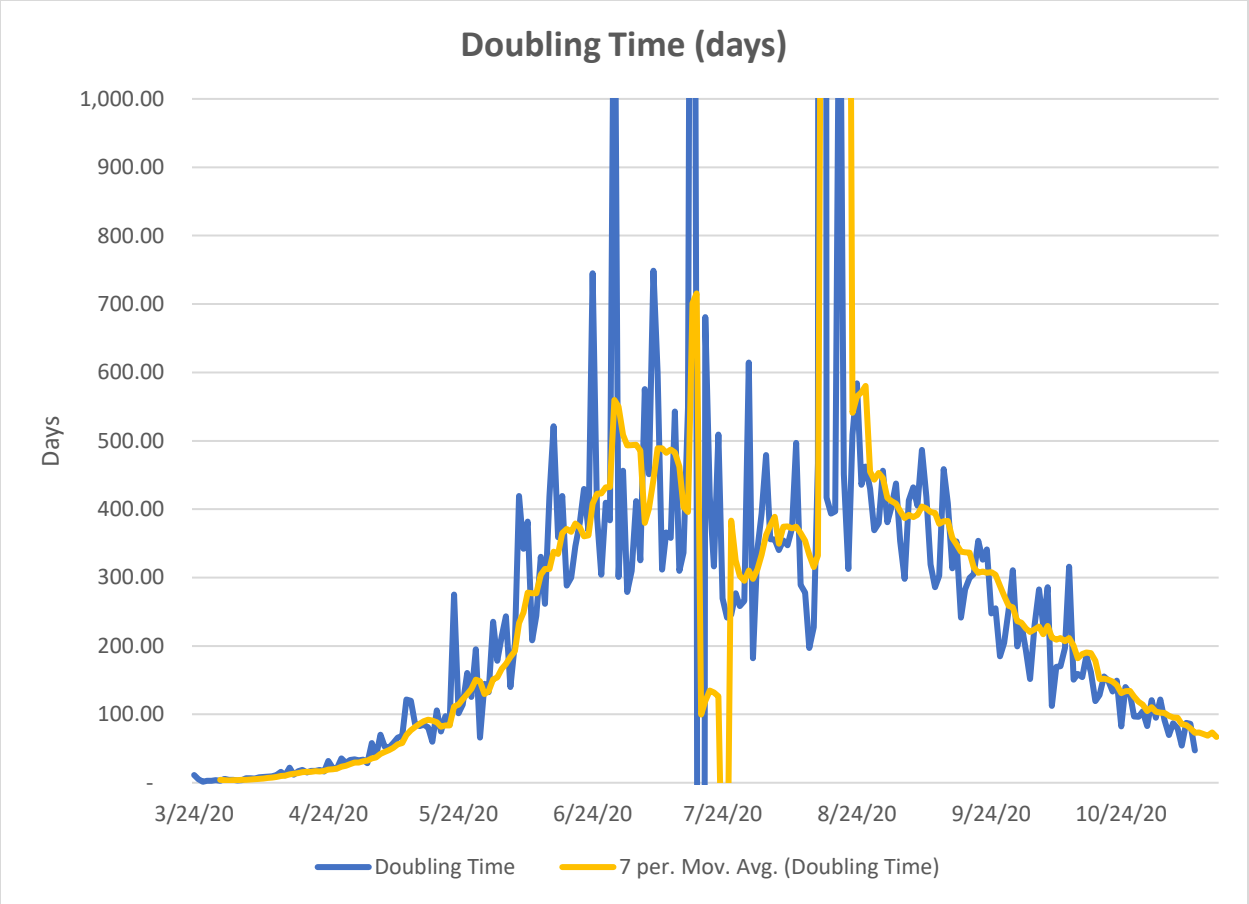
Finally we have the daily LTC and non-LTC deaths. We have done this starting in early July. One would have assumed that LTC facilities would have been quarantined and secure but as one can see LTC deaths continue.



The key observation above is that LTC deaths have continued since early July despite the knowledge that they dominated the mortality.

2.3 Doubling Time

Finally, we calculate the doubling time on a daily basis and depict this below. Doubling time is a useful metric when the increase is substantial as we see now.



The above depicts the decreased doubling time and it demonstrates that with this data we are back in the April time frame.

2.4 Some Demographics

Slowly we are seeing demographic data and this includes such information as sex, age, race, and towns. The chart below depicts the relative percent of infected by race. Before discussing let us review the statistic.

First, we have data that gives the ratio of infected by class to all infected. Namely:

$$R_i = \frac{Number\_Infected\_by\_Class}{Total\_Infected} = \frac{I_i}{\sum_{k=1}^{N} I_k}$$

Then we have the percent or ratio of population by class to total population:

$$Q_i = \frac{Number\_Population\_by\_Class}{Total\_Population} = \frac{P_i}{\sum_{k=1}^{N} P_k}$$

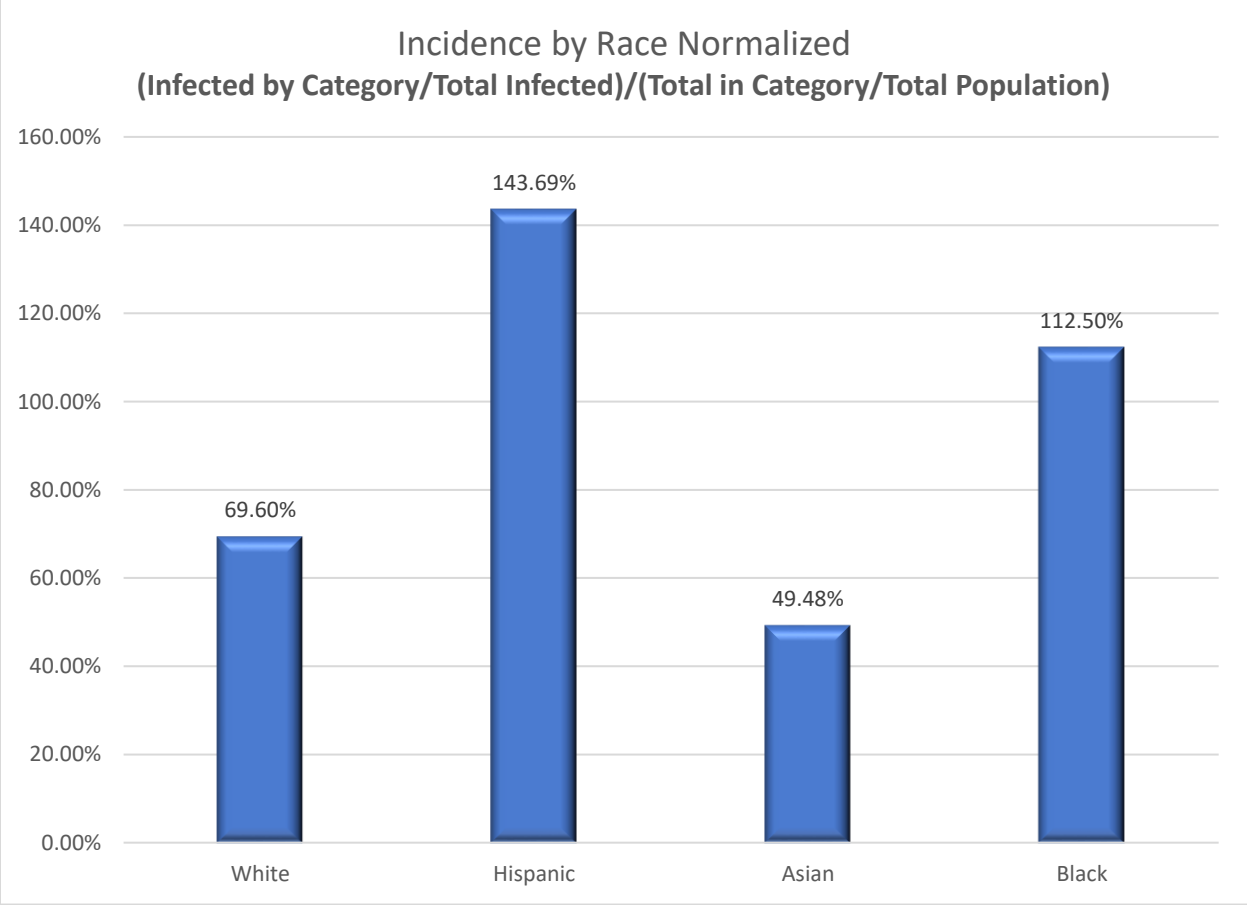
We then define the term:

$$M_i = \frac{R_i}{Q_i}$$

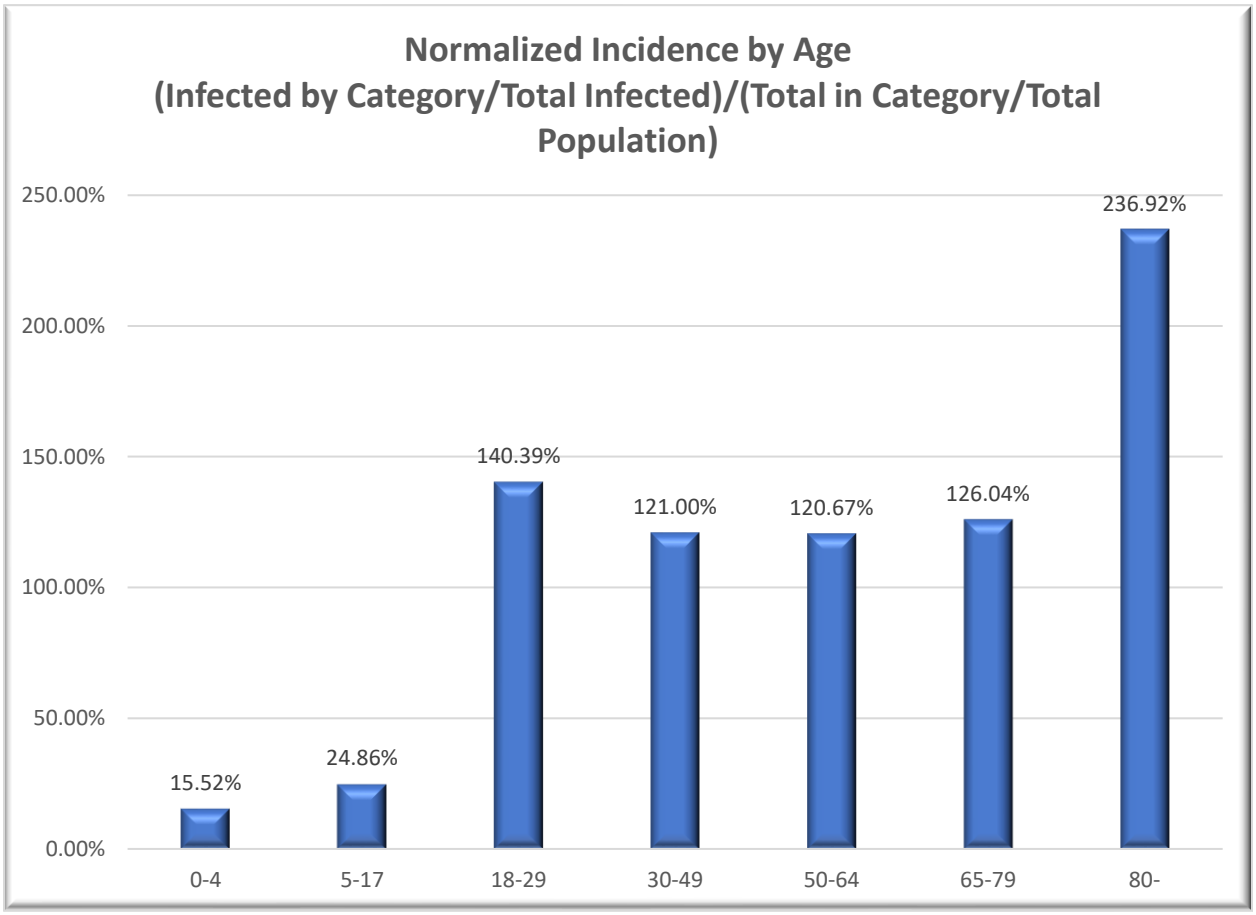
or

$$M_i = \frac{Number\_Infected\_by\_Class}{Number\_Population\_by\_Class} \frac{Total\_Population}{Total\_Population\_Infected}$$

Thus this metric yields an infection by class normalized by the gross infection rate. We depict this below. The chart is a relative metric. It does show significant class differences. Namely it shows that Hispanics are significantly higher than all other races. It shows that Asians are almost one third Hispanics. One could assume that this is a result of immigrant status and socioeconomic status as well. The specifics are unknown but should have been a part of the State's study which is lacking.



Why is this important? Simply it gives one a target for remediation. Namely immunizing the most exposed. Now we do the same for age brackets using the same metric. This is equally normalized. The result is below.



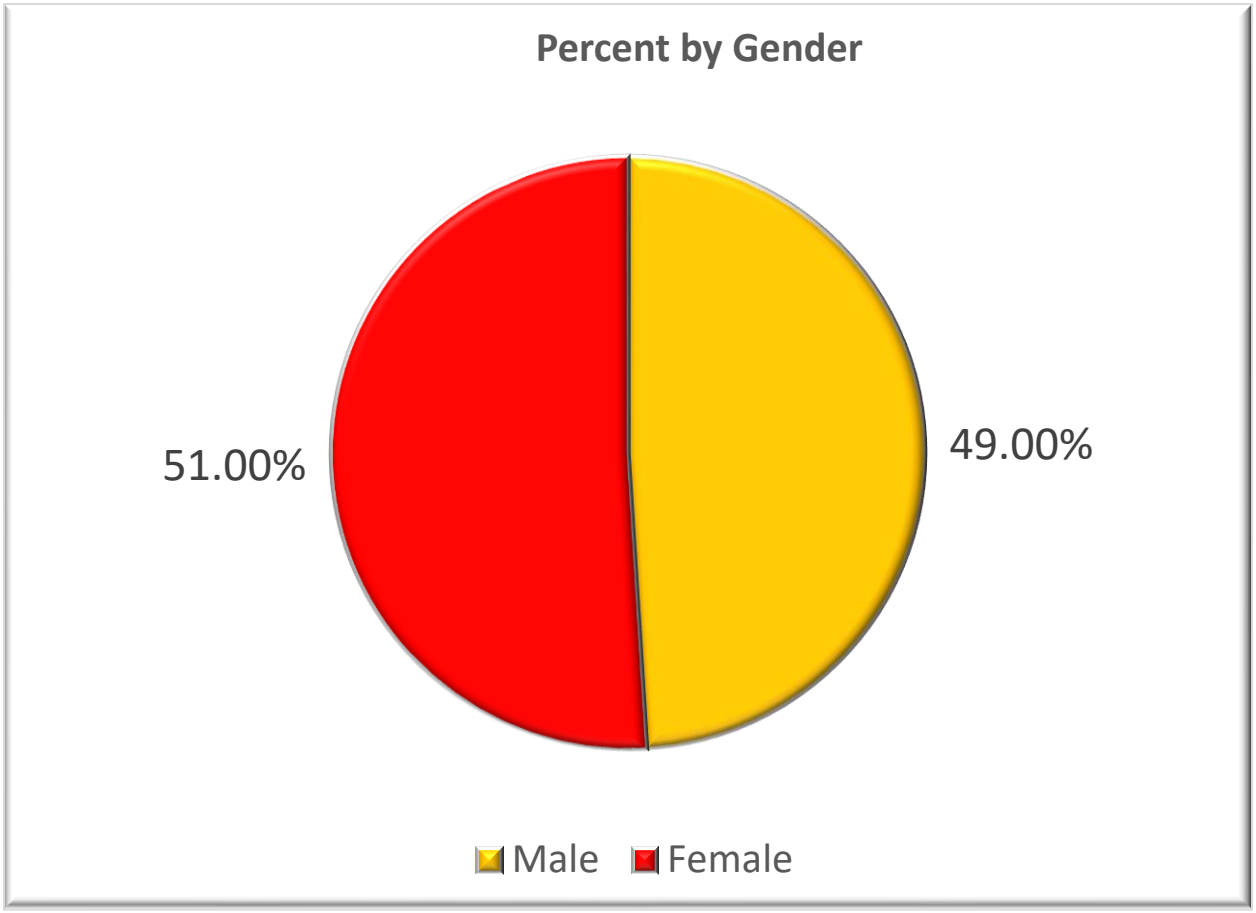
What does this tell us? Simply:

1. The State sent infected patients into closed Long Term Nursing Care, LTC, facilities and the result is that 50% of the deaths were from that group alone! Regrettably it continues.

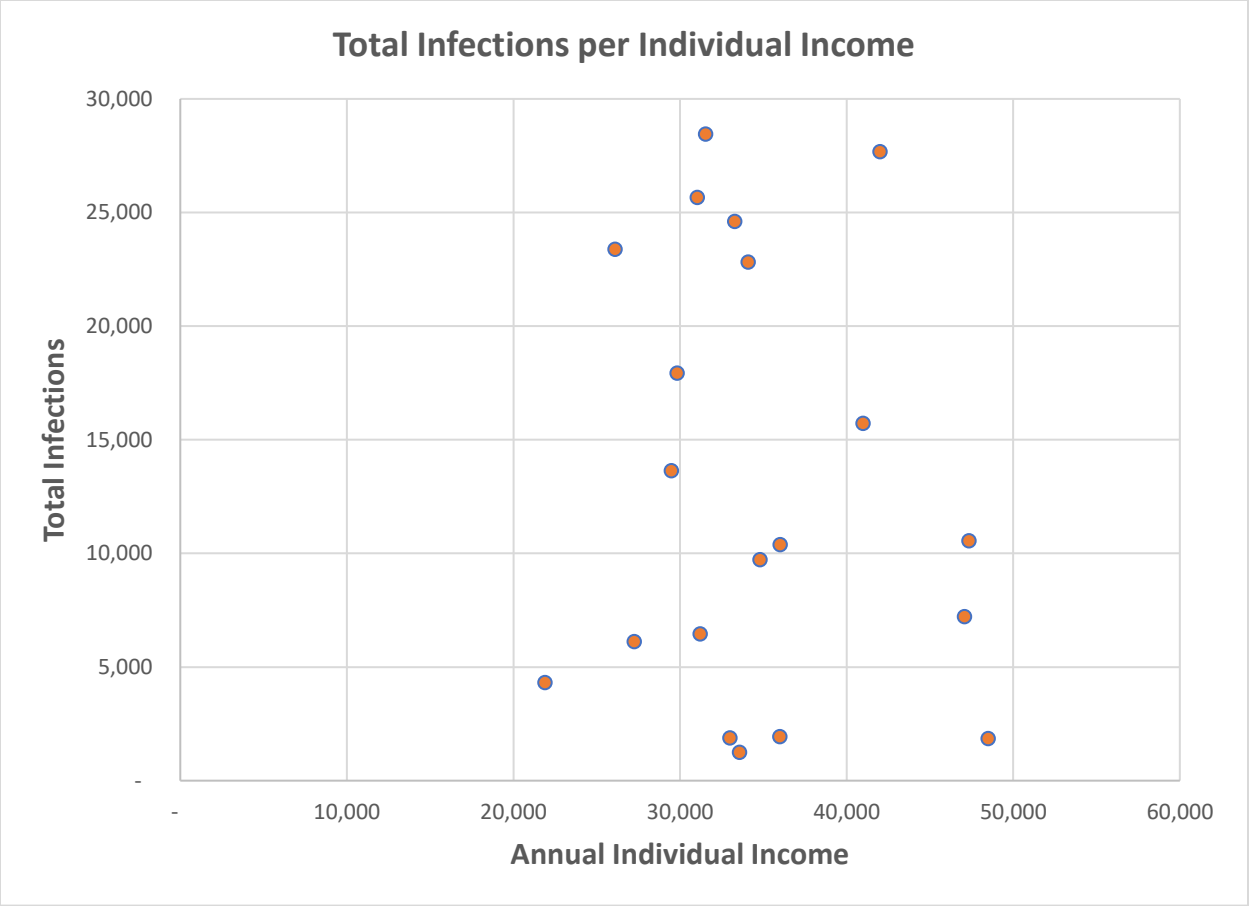
2. The 17 and under group seem not to be infected. However this may be an artifact of poor testing. we suspect that they are major carriers yet with higher immune systems do not present for testing. If the State had mandated weekly testing of all school age children we would see a totally different picture.

3. The data shows that from 18 to 80 the incidence is the same.

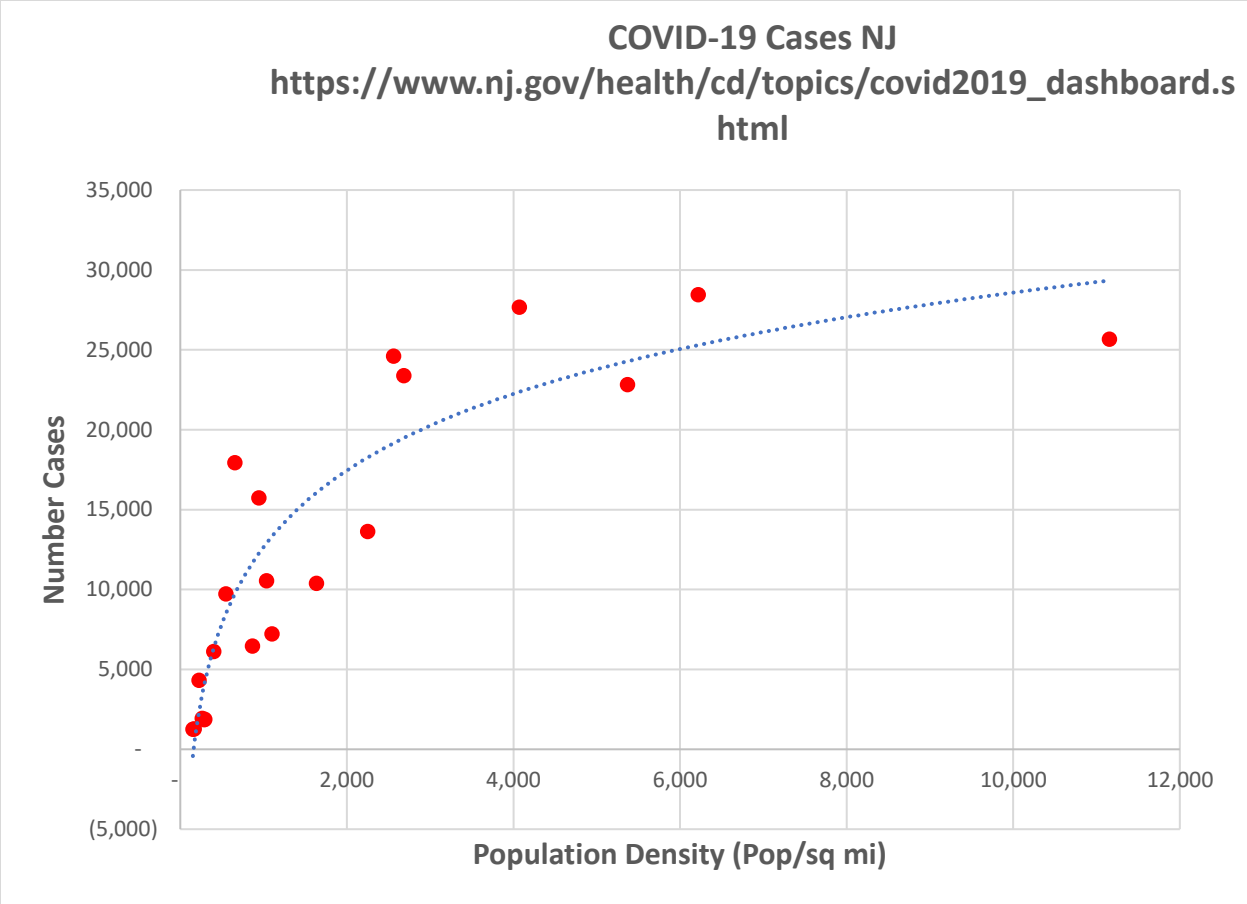
Below we show the data indicating infections slightly favor females to males.



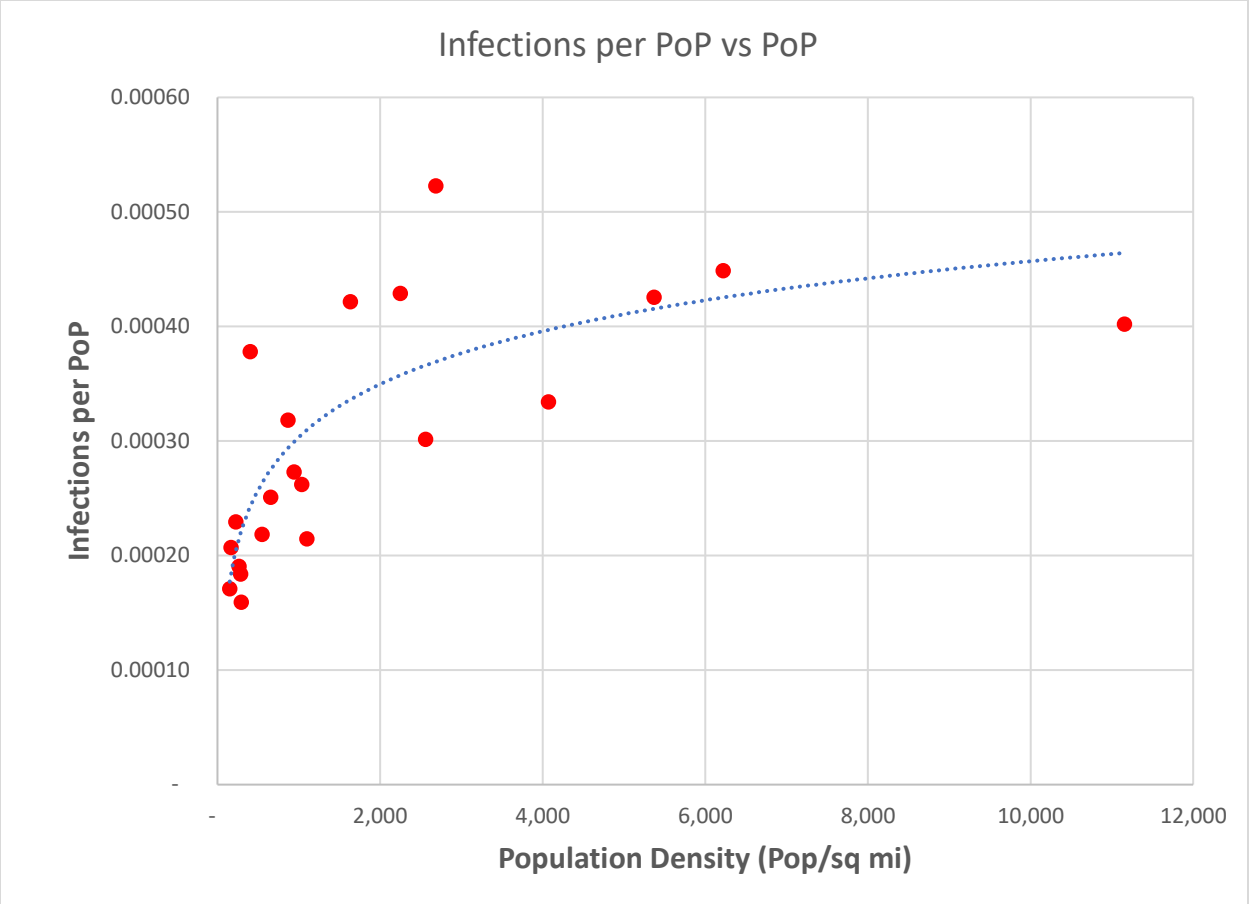
Now we asked what is the impact of income? This is shown below where we see little if any impact. Namely income has not material effect on infections.



However, population density does have an effect if we were to consider total infections versus population.



Now we can also plot this on an infections per PoP basis vs PoPs.



Clearly the same effect is seen. Namely low PoP density means low infection density.

2.5 TESTING

Testing is more than just performing a test, getting a result and at some time reporting the result. One of the major defects in the current COVID outbreak is the lack of truthful and/or usable data. The major factors which should be available in a testing protocol must be:

1. Timeliness: This is a broad category of time related issues. Such as:

a. when was the patient first requesting a test
b. when was the test scheduled
c. when was the test performed
d. when were the test results finalized
e. when were the test results reported

One of the things we have seen again and again with the test data is the delays in reporting and the bundling of test results that appear as mini outbreaks. The most critical problem here is shown below regarding the timeline.

In the above, the critical period is the one described. It may be two weeks. During that time the individual is possibly spreading the virus. A possible solution is mandatory testing of those at possible risk. A goal should be to expand testing and reduce the exposure time. After nine months this issue has yet to be addressed.

2. Demographics: This is a description of the demographic profile of the patient. Data such as:

a. Age
b. Occupation if any
c. Race
d. Gender
e. Ethnicity
f. Family setting
g. Income
h. Education

One can agree that HIPPA regulations should be observed but some form of anonymization can be performed. As we noted above with the limited data we can pinpoint certain demographic and geographic targeting.

3. Medical History: This is a history of patient and family histories. The data should include, subject to HIPPA compliance:

a. Pre-existing conditions
b. Presenting symptoms
c. Family history
d. Patient history

4. Testing Protocol: Details on what tests were performed and the details regarding the efficacy of the test protocol.

a. Test Assay and Vendor
b. Test Location
c. Test Laboratory
d. Test False Negatives and Positives
e. Person doing test
f. Location of Test analysis

and so forth.

Now, a *Technology Review* article looks at this issue and suggests a Government controlled review. They state[5]:

Getting this data means going to the health department website of each jurisdiction in question (and the neighboring ones), pulling up the information separately, and then trying to collate it all. You'll have to pray the information is up to date, since there's no guarantee. And you might even have to contact the departments directly and make a special request if you're looking for numbers and information not readily available on their websites. The entire process will be a long, drawn-out, frustrating affair. And you might not even get what you want. Why? Because public health is a decentralized system in the US. In the case of covid-19, there's no consistent standard for how states should collect and report the data. Individual states and their own health departments decide how they want to handle testing—including how to collect, organize, and report the results. And that can be a problem....

Most experts agree that in an ideal situation, the federal government would lead the management of public health data for a crisis like this—but that is highly unlikely to happen. Given that some models suggest we'll need to implement response measures against the pandemic into 2022, though, Miri doesn't think it's too late to push forward a national initiative. It's just a matter of funding such measures, and persuading states to accept more oversight. That's not always an easy sell, but the pandemic's effects may have softened state officials up a bit.

What we need is an open, dynamic, transparent approach.

Notwithstanding, a common database is critical and the data should be open to all comers. There are many minds out there who can examine the data from a different and possibly beneficial perspective. Governments have demonstrated an inability to produce. Worse yet, the WHO has lost all credibility that no one believes anything they say or worse, whatever they say must be false. Likewise, the CDC cannot produce or disseminate timely data. The MMWR is a classic example of a weekly report frozen in a political quagmire.

[5] https://www.technologyreview.com/2020/05/07/1001311/how-to-manage-coronavirus-testing-data-collection-management-reporting-state-health-departments/

3 VIRAL BASICS

Let us begin with a summary presentation of viruses. The intent is to emphasize the critical factors in the pandemic of 2020[6].

3.1 FAMILIES AND GENUS

There is a multiplicity of viruses in nature and a large group impact humans. The classification is in families and genus. The basic classification is between DNA and RNA viruses. There are approximately 6 major DNA virus families and 15 RNA families. The Corona virus is in the RNA family. Namely the virus is an RNA strand.

They can be broken down into single and double strands. Thus, Corona is a single strand RNA virus. Moreover, the strands can be positive or negative. Positive strands have tails on the 3' ends and have a small virus protein on the 5' end. Negative strands are the opposite. Corona virus are thus single stranded positive RNA viruses.

The virus is also enveloped. The envelope contains three major proteins. They are: (i) a transmembrane glycoprotein, (ii) a surface peplomer which neutralizes antibodies, does receptor binding, membrane fusion, and other activities, (iii) a haemagglutinin and esterase activity unit. The genome size is quite large, about 30,000 bases.

3.2 INFECTION

Infection with the Corona virus is through nasal passages of the nasopharynx. It results from aerosol particles from an infected person or through contact with surfaces infected by similar aerosols. Many of the specifics of the infection process are still unknown. One suspects that it is based upon aerosols. On a personal note, my grandmother spent a decade at Sea View Hospital in New York City managing TB and Spanish Flu patients from 1910 through 1921. Her constant advice was to wash your hands, don't touch your face, cover your mouth, don't touch things. She survived while a massive number of her patients died. we think we learned a lesson. But there is still no scientific evidence just decades of experience.

Along comes the CDC. They now state[7]:

COVID-19 is thought to spread mainly through close contact from person-to-person. Some people without symptoms may be able to spread the virus. We are still learning about how the virus spreads and the severity of illness it causes.

Person-to-person spread: The virus is thought to spread mainly from person-to-person.

---

[6] See the following written in March 2020 as the pandemic began:
https://www.telmarc.com/Documents/White%20Papers/173Corona.pdf

[7] https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/how-covid-spreads.html

1. Between people who are in close contact with one another (within about 6 feet).

2. Through respiratory droplets produced when an infected person coughs, sneezes, or talks.

3. These droplets can land in the mouths or noses of people who are nearby or possibly be inhaled into the lungs.

4. COVID-19 may be spread by people who are not showing symptoms.

The virus spreads easily between people: How easily a virus spreads from person-to-person can vary. Some viruses are highly contagious, like measles, while other viruses do not spread as easily. Another factor is whether the spread is sustained, which means it goes from person-to-person without stopping. The virus that causes COVID-19 is spreading very easily and sustainably between people. Information from the ongoing COVID-19 pandemic suggests that this virus is spreading more efficiently than influenza, but not as efficiently as measles, which is highly contagious. In general, the more closely a person interacts with others and the longer that interaction, the higher the risk of COVID-19 spread.

The virus may be spread in other ways: It may be possible that a person can get COVID-19 by touching a surface or object that has the virus on it and then touching their own mouth, nose, or possibly their eyes. This is not thought to be the main way the virus spreads, but we are still learning more about how this virus spreads.

This is what we said in early March and what my grandmother said in 1945! This is the nth revision of the CDC assessment. There seems to be a serious and chronic problem there. One wonders when it can and must be corrected?

As an added note, as we had also discussed, the virion travels in an encased aerosol, namely an air-filled water encased bubble that moves about with Newtons laws of motion as well as following Archimedes principle by floating. The aerosol also has thermodynamic effects as well with Brownian motion effects resulting from random collisions[8]. Thus aerosols "linger" depending upon a multiplicity of factors. Just what makes for lingering aerosols depends. There is a significant body of knowledge in atmospheric aerosols but virion containing ones, not so much.

What is lacking is good quality physical and clinical research. Unfortunately, the CDC does not seem as advance as my grandmother back in 1918.

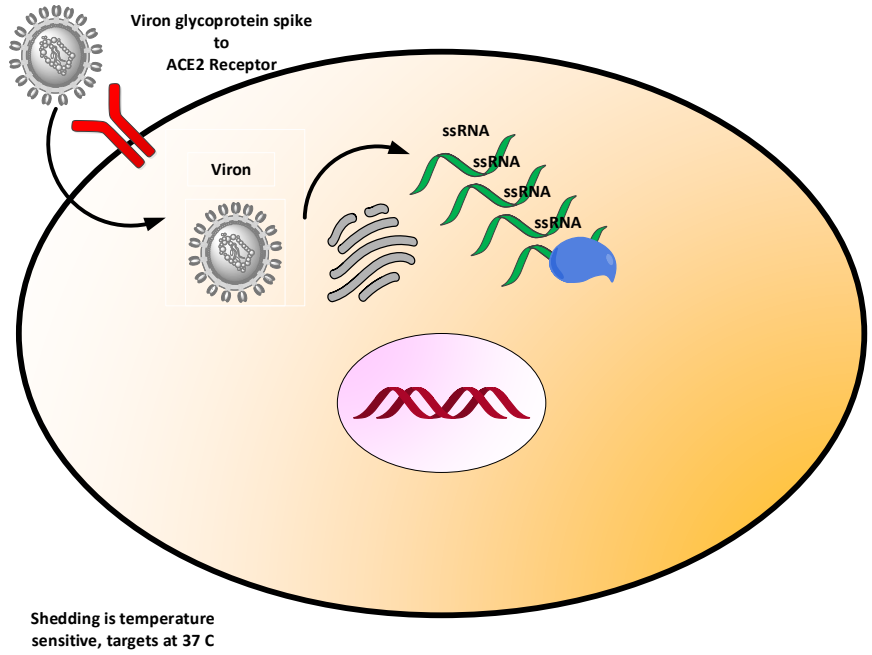
3.3 CORONA SPECIFICS

Let us now examine the specifics of corona. Corona are large positive single strand RNA viruses with surface ligands that bind to ACE2 receptors on epithelial cells and then progress to multiply

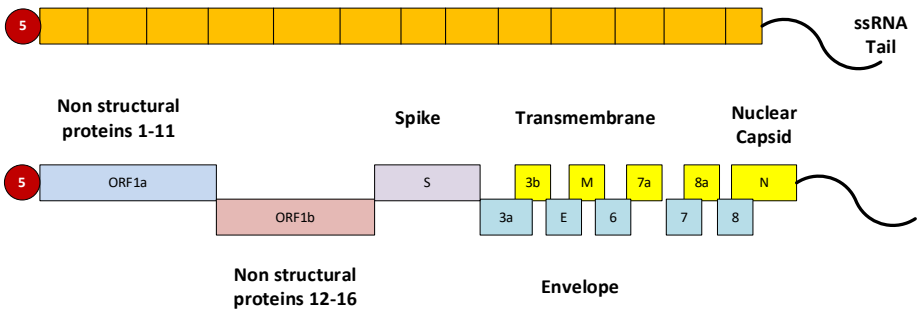
[8] see Seinfeld and Pandis, Atmospheric Chemistry and Physics, Wiley, 2016, Chapters 9-10

internally at a temperature of 37 C. Unlike rhinoviruses which are epithelial but multiply at 35 C, the nasal passageways, the corona needs to move to the lungs and the higher temperature to fully expand.

The figure below summarizes this virus. The RNA is about 30,000 base pairs and when translated can produce eight operable regions for the generation of proteins or RNA replication.



These regions of the RNA of the Corona virus are depicted below. First the ssRNA is combines with it complement creating a double strand and within that double strand we have sub units which will give rise to the protein elements necessary for its replication. Key to that will be a polymerase allowing for the production of the elements.



The details of these eight elements are shown as below. The RNA has a protein on one end and a tail at the other end. The eight active sections are depicted including the two replicase regions essential for reproducing the ssRNA and other smaller segments involved in the process. There is a reasonable understanding as to the virologic processes associated with the COVID virion. The replication of the virus is described by Oxford et al (5th Ed):

Virions initially attach to the cell plasma membrane through specific receptors. These have been identified for several coro-naviruses; for example, human coronavirus uses the membrane-bound metalloproteinase, aminopeptidase N (APN), whereas OC43 simply binds to sialic acid groups on cell-surface proteins. SARS CoV uses the host-cell receptor angiotensin-converting enzyme 2 (ACE2) to gain entry into cells whereas MERS CoV uses the host receptor dipeptidyl peptidase 4 (DPP4). Uptake into cells is rapid and temperature-dependent, involving fusion with the plasma membrane or via endocytosis followed by a spike-mediated fusion in the endosome. Large multinucleated giant cells, syncytia, can be formed both in the laboratory and in an infected host.

Once released into the cytoplasm the virus positive-strand RNA is translated directly into two polypeptides: ORFla and ORFlb at the 5' end of the genome. These are processed to form a replicase-transcriptase complex that possesses RNA polymerase activity. The RNA polymerase transcribes a full-length negative RNA strand, which acts as the template for transcription of multiple subgenomic virus mRNAs.

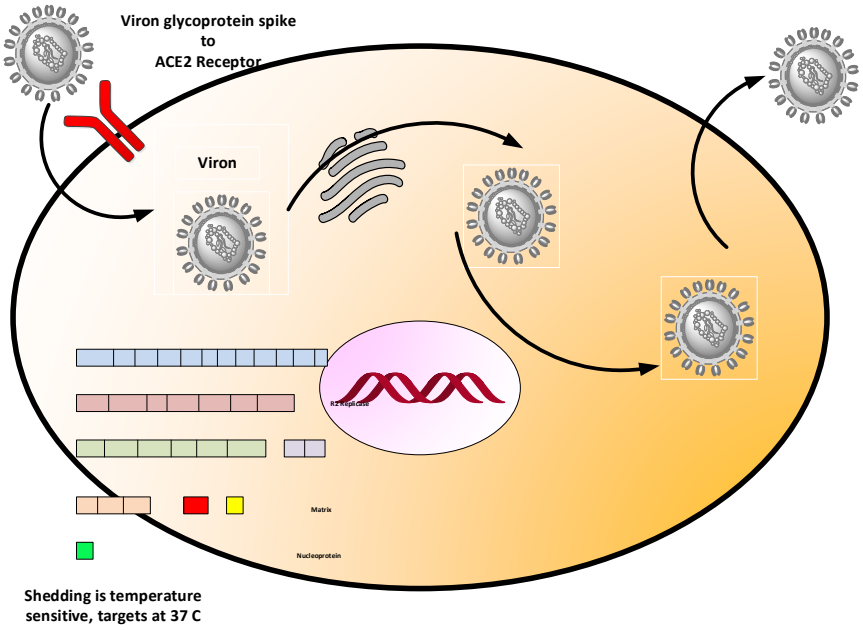
Coronavirus mRNAs are unusual in that they all terminate at the common 3' end of the genome, but start at various places from the 5' end to produce a nested set of 3' co-terminal transcripts. Each of the eight mRNAs, except for the smallest, therefore encode for multiple proteins, with the longest one being, in effect, full-length coronavirus genome RNA and the others in descending order of size being S, E, M, and N. Generally, each subgenomic virus mRNA is the template for translation into one protein. There are 16 non-structural proteins (l-16nsp), some of which have proteinase functions or are polymerases, including RNA-dependent RNA polymerase (nspl2) and endoribonuclease (nspl5).

Virus proteins that constitute the virus particle, namely N, M, and S, are produced in the infected cell and new virion assembly occurs initially in the cytoplasm on smooth-walled vesicles located between the ER and the Golgi known as ERGIC (endoplasmic reticulum Golgi intermediate compartment).

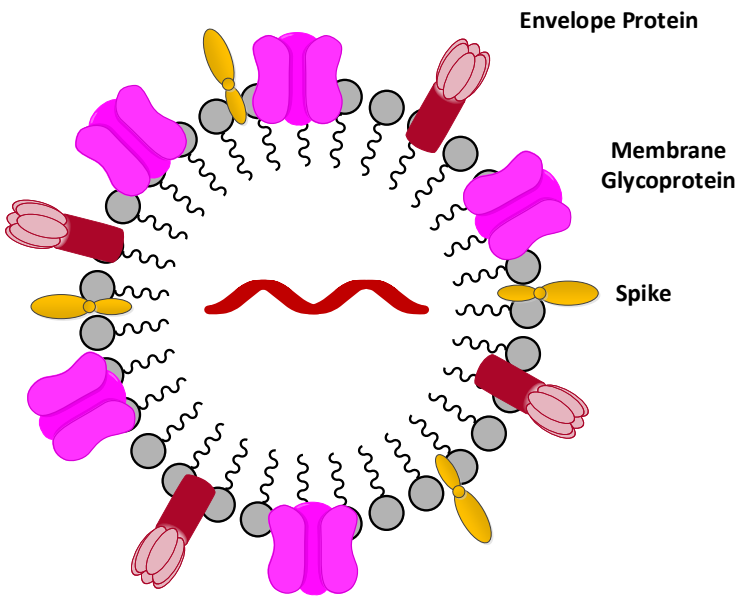
There newly formed RNP interacts with the M protein from the ER, and M interacts with the S and other proteins to form the infectious virus which buds into the Golgi, thereby acquiring a lipid envelope. Envelope proteins are glycosylated in the Golgi. Virions are released by fusion of smooth-walled virion-containing vesicles with the plasma membrane. As with other RNA viruses, the lack of proofreading functions in the virus RNA polymerase leads to a high rate of mutation in the new virus genomes.

The very long genomes, together with the discontinuous RNA replication, can favour recombination leading to new genotypes with varying pathogenicity. There remains also the possibility of recombination between zoonotic corona viruses and between human viruses. Recombination can allow corona viruses to rapidly evolve and adapt to new ecological niches.

We demonstrate the above in the figure below:



The details of the virion appear below with the prominent Spike protein on the surface surrounded by a lipid layer. The single stranded RNA is contained inside.



As we will note, the above structure becomes the target for a vaccine development. Specifically the unique surface proteins. As we shall note, the spike protein is specific to this virus and if we can then design an antibody to attack that site then we can utilize the immune system itself.

4 IMMUNE SYSTEM BASIS

We present a very brief but essential overview of the workings of the immune system. The reason is that with vaccines we want to use the body's own immune system to attack the invader. To do this we need to identify an antigen or a protein unique to the invader and identifiable by the immune system. Then if the immune system can function in its antigen presenting cells, APC, the antigen gets presented to the immune system B and T cells. The B cells take off and generate antibodies, namely proteins which are identifiable by other immune cells and attach to the viral antigen. This one end of the Ab attaches to the virus and the other end to an immune cell which is then activated to kill the virus. Thus we are off and running.

4.1 ANTIGENS

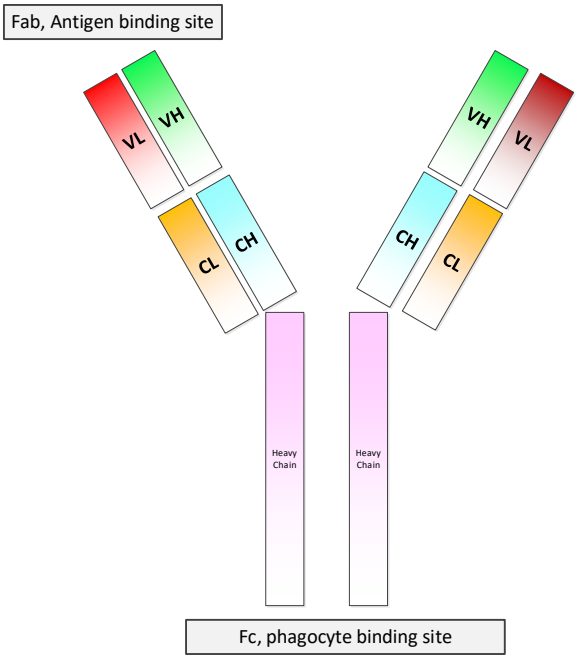
Antigens (Ag) are molecular markers on cells that can be detected by T cells or by an antibody. In many cases the antigen is a cell surface protein or fragment of a protein. Antigens are used to identify some aberrant cell and then to activate the immune response. In the case of the Corona virus the Ag of interest is the spike protein we demonstrated above.

4.2 ANTIBODIES

Antibodies are the initiators of the adaptive immune system. They can be self-generated or externally generated. External Ab have been used therapeutically in treating COVID-19. Self-generated Ab require some form of a vaccine to initiate the process in the adaptive immune system. As Abbas et al note:

Type of glycoprotein molecule, also called immunoglobulin (Ig), produced by B lymphocytes that binds antigens, often with a high degree of specificity and affinity. The basic structural unit of an antibody is composed of two identical heavy chains and two identical light chains. N-terminal variable regions of the heavy and light chains form the antigen-binding sites, whereas the C-terminal constant regions of the heavy chains functionally interact with other molecules in the immune system. Every individual has millions of different antibodies, each with a unique antigen-binding site. Secreted antibodies perform various effector functions, including neutralizing antigens, activating complement, and promoting leukocyte-dependent destruction of microbes.

We demonstrate a typical IgG form below:

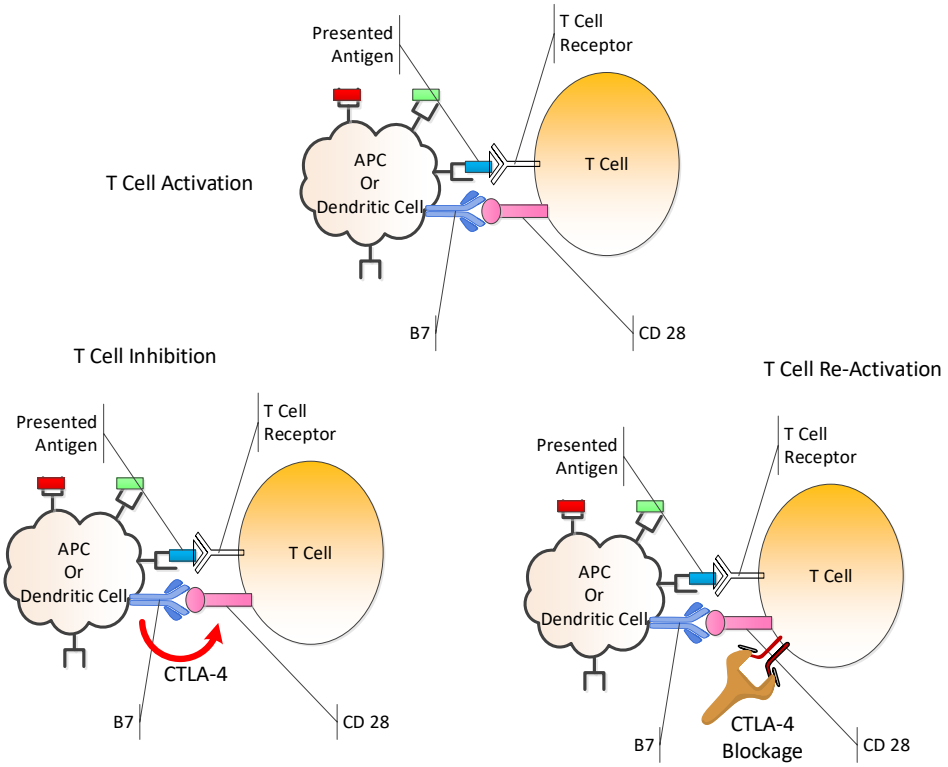


Note the Fab end binds to the antigen on the target cell and the Fc end binds to an immune cell. There are multiple Fc each with a different immune cell binding capability. The Ab are generated via the B cells upon the APC cells presenting the targeted Ag. The Ab generated by a B cell will leave a B cell with memory for some period. It should be remembered that a patient with the virus can be given the specific Ab and the virus will be attacked while the dosage of Ab remain relatively high. Once they are depleted the virus can begin again. However if the B cell is activated and generates its own Ab, then Abs are created until the virus is eliminated and the capacity to regenerate them lasts for a period of time.

Thus the key issue with a vaccine is to generate the targeted Ab for the specific Ag. This is done in a normal process if the Ag can be properly recognized.

4.3 Antigen Presenting Cells

We now briefly examine the antigen presenting system. First, we have antigen presenting cells, cells that wander around looking for "stuff" that does not belong, like viruses. We demonstrate several differing actions below.

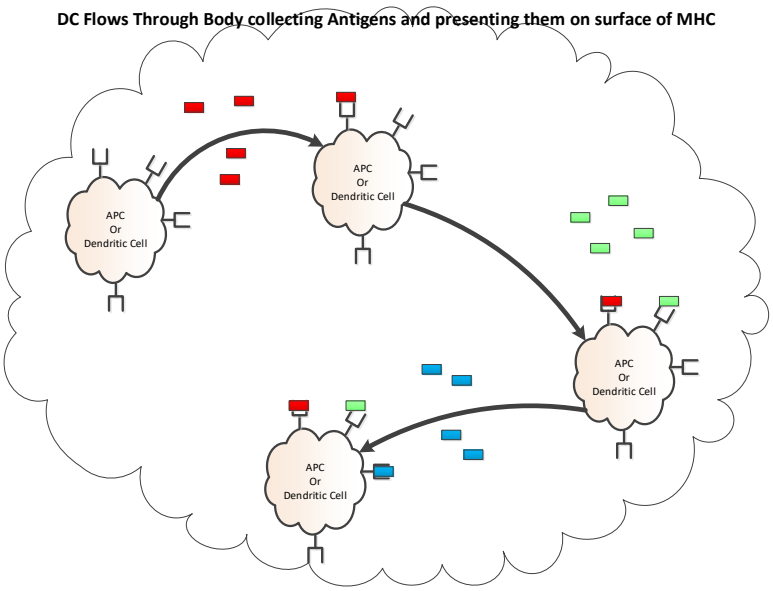


Here we have an APC presenting the Ag to a T cell. The T cell receptor, TCR, recognizes the Ag. There can be an inhibition but not generally in a viral case. They have proteins on their surface that work one of two ways. We focus on those with MHC II proteins.

MHC I
All Cells
When something
NOT OK IN Cell

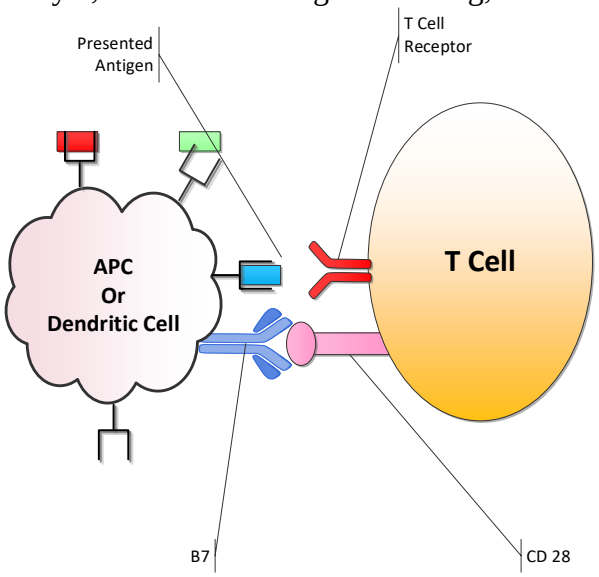
MHC II
APC Cells Only
Tells something
NOT OK Outside
Cell

Now as these APCs move about they collect proteins which we call antigens. They take these Ag and present them to the immune cells.



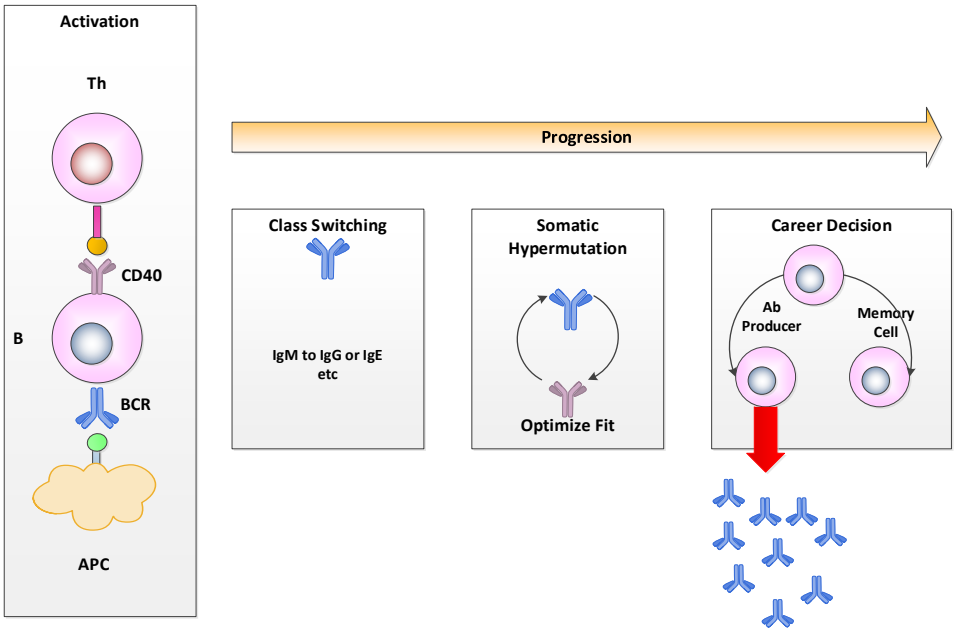
4.4 B AND T CELLS

The B and T cells are the basic elements of the adaptive immune system. The T cell is one such immune cell and one which does a great deal to kill off the invader. Thus we need to get that T cell, a cytotoxic T lymphocyte, CTL activated against the Ag, and thus against the invader.

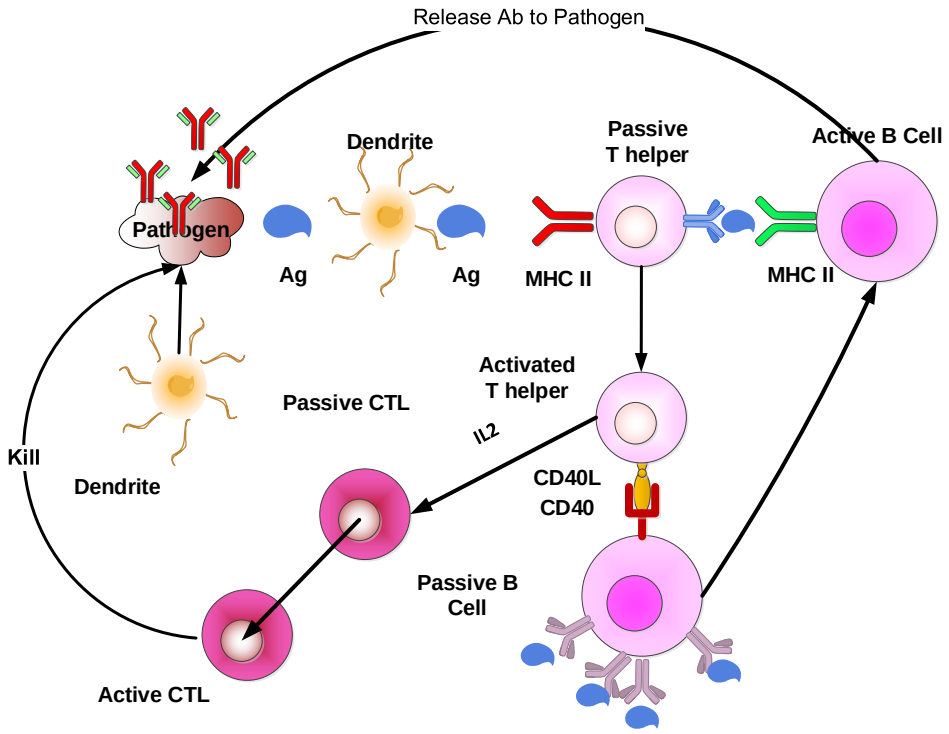


CD28 (Cluster of Differentiation 28) is one of the proteins expressed on T cells that provide co-stimulatory signals required for T cell activation and survival. T cell stimulation through CD28 in addition to the T-cell receptor (TCR) can provide a potent signal for the production of various interleukins (IL-6 in particular). CD28 is the receptor for CD80 (B7.1) and CD86 (B7.2) proteins. When activated by Toll-like receptor ligands, the CD80 expression is upregulated in antigen presenting cells (APCs). The CD86 expression on antigen presenting cells is constitutive (expression is independent of environmental factors). CD28 is the only B7 receptor constitutively expressed on naive T cells. Association of the TCR of a naive T cell with MHC:antigen complex without CD28:B7 interaction results in a T cell that is anergic.

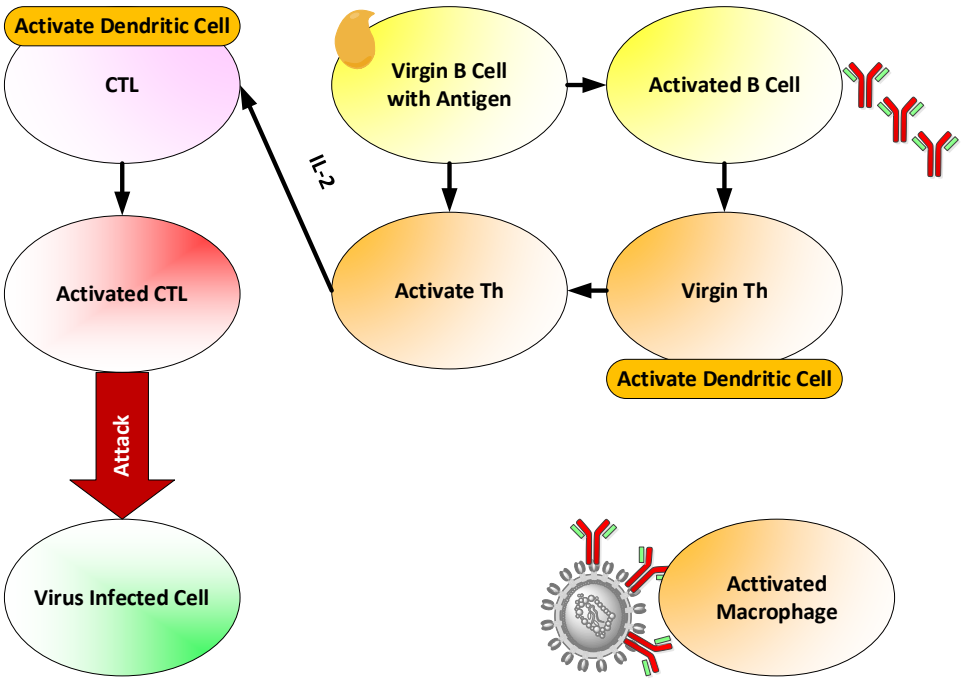
A second path is the B cells and the generation of antibodies, Ab. Ab are generated by the B cells and they go out and cover invading cells as markers. The B cells are the facilitators of the generation of the specific antibodies. The process is complex and we leave it to the reader to explore that separately if unfamiliar with it. Now the diagram below is a general description of the interaction of B and T cells. The T helper cell interacts with the B cell which has interacted with an APC. The result is a progression wherein the Abs are generated and optimized to fit the presented Ag. The result is a set of B cells emitting massive amounts of Abs and a remainder set of B cells remembering just in case of next time.



The overall process is shown below in simple form. This is an enhancement on all of the elements which we presented earlier.



We can summarize this as below.



The challenge is to create an Ag without creating the disease. Classically this was done with attenuated viruses and letting the immune system pick and choose the Ag to start the process. Pasteur and his work on rabies was the first classic example of this in some detail. Smallpox is an earlier example using a cow pox exposure.

As Tregoning et al note regarding vaccines and T cells:

The T cell response is important in the control of other respiratory infections, and therefore likely to be important in COVID-19 [11]. Models of SARS-CoV-1 indicate that T cells can be protective. CD4+ T cell depletion in mouse models delayed viral clearance and enhanced disease; similarly, T cell transfer resulted in rapid viral clearance and disease amelioration. SARS-CoV-1-specific CD8+ T resident memory were protective in a mouse model in the absence of antibody. T cell memory can be long-lived; SARS-CoV-1 T cells were detected 4 years after infection.

For SARSCoV-2, T cell responses have been observed to a range of antigens, including S, M, N and other ORFs. SARSCoV-2-specific T cells have been detected in individuals who had asymptomatic or mild COVID-19 and SARS-CoV-2-specific T cells have been observed in contacts of infected individuals. Patients suffering from COVID-19 had fewer T cells than healthy controls.

T cells, especially CD4+ T cells, can influence the immune response through the production of cytokines, and elevated cytokines have been associated with exacerbated disease. The skewing of the CD4+ T cell response is likely to be important. T helper type 1 (Th1) responses are central to the successful control of SARS-CoV-1 and MERS-CoV. Th17 responses have been speculated to be deleterious, and increased Th2 cytokines were seen in severe disease. Regulatory T cells are important in the resolution of infection, and were observed to be elevated in COVID-19 patients. Circulating follicular T helper cells, important in defining recall antibody response to infection, have been observed in a small number of individuals with COVID-19. It is not clear whether the 'cytokine storm' is a cause or effect of disease; understanding this relationship is critical in monitoring vaccine safety.

In a similar manner they note regarding Abs:

The humoral response is pivotal in later stages of infection and helps to inhibit subsequent reinfection. Virus-specific antibodies were detectable in 80– 100% of SARS-CoV-1 and MERS-CoV patients 2 weeks after onset of symptoms, with delayed antibody responses associated with more severe disease.

A number of studies have been performed to try to more clearly understand the antibody response to SARS-CoV-2; a systematic review of studies on antibody to coronaviruses observed that antibody was rarely seen in the first 7 days of infection, but rose in the second and third weeks postinfection. It is unclear whether antibodies correlate with COVID-19 severity. Antibodies are likely to be an important part of vaccine-induced protection. In SARS-CoV-1, the antibody response is short-lived [immunoglobulin (Ig)M and IgA responses last less than 6 months and IgG lasts approximately 1 year]; this is possibly the same for SARS-CoV-2.

Human challenge studies using non-COVID-19 coronavirus strains suggest that higher antibody levels correlate with protection. These challenge studies have also suggested that reinfection is possible, but the dose in challenge studies may be higher than experienced during natural infection. Two recent studies have observed natural reinfections with SARS-CoV-2, one asymptomatic and one symptomatic, although this is in the context of more than 25 million recorded cases globally, suggesting that it is a rare event. Because of the overlap between SARS-CoV-1 and SARS-CoV-2 spike proteins, antibodies could be cross-neutralizing.

However, the most potent specific, neutralizing monoclonal antibodies against the receptor binding domain (RBD) of SARS-CoV-1 did not bind to the spike protein of SARS-CoV-2. One promising observation is that isolated neutralizing antibodies have minimally mutated VDJ genes, which make inducing them possible with fewer rounds of vaccination. Most attention has focused upon neutralizing IgG antibodies in the serum, but other antibody-mediated mechanisms may be important in disease pathogenesis.

Fragment crystallizable (Fc) and Fc receptor (FcR) interactions can regulate the inflammatory response and the SARSCoV-2 virus–antibody complex could potentially trigger such FcR-mediated inflammatory responses, causing acute lung injury. The IgA response may be important in determining disease severity of COVID-19 patients, but remains relatively unexplored so far.

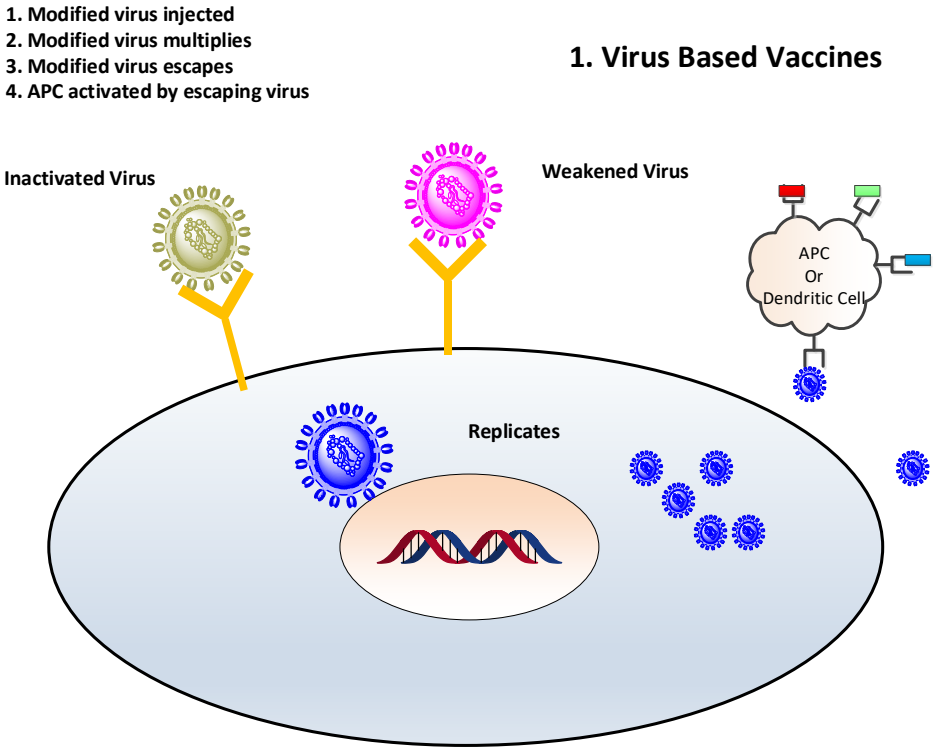
5 VACCINE OPTIONS

Vaccines have been around for over a century. Some even more in a rudimentary form. Let us take a brief look[9]. This is not a complete precis to vaccines but it is a first order introduction. Our ultimate focus will be on mRNA vaccines as we shall demonstrate.

5.1 VIRUS BASED

Now there are multiple ways to generate a vaccine to kill off the invader. The classic manner is shown below. We use inactivated or weakened viruses and hope they stay that way. We inject them and then wait for an immune response. This is done by generating live virus elements oftentimes in eggs. This is a long and costly process, needless to say, using a lot of eggs.

In addition we can used attenuated or killed viruses. The driver is the antigen recognition and the initiation of antibody proliferation. We depict this approach below:

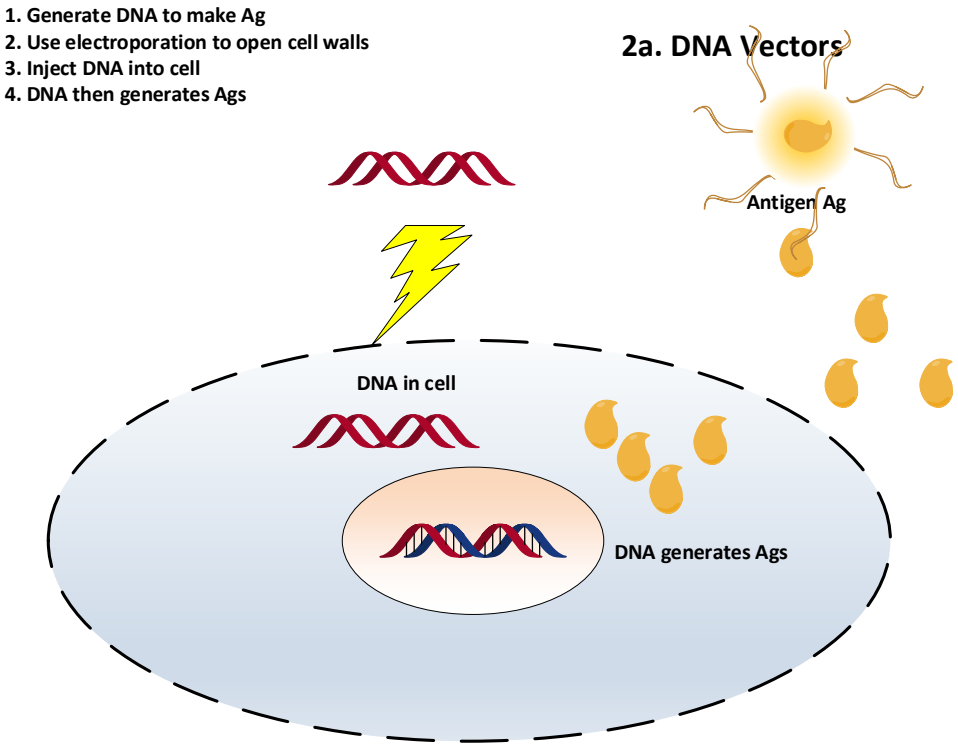


The classic example is the Salk and Sabin polio vaccines. The Salk vaccine was an inactivated form which required injection and the Sabin form was a weakened virus taken by mouth.

[9] https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html This is a list of the major players and their approaches.

5.2 DNA VECTORS

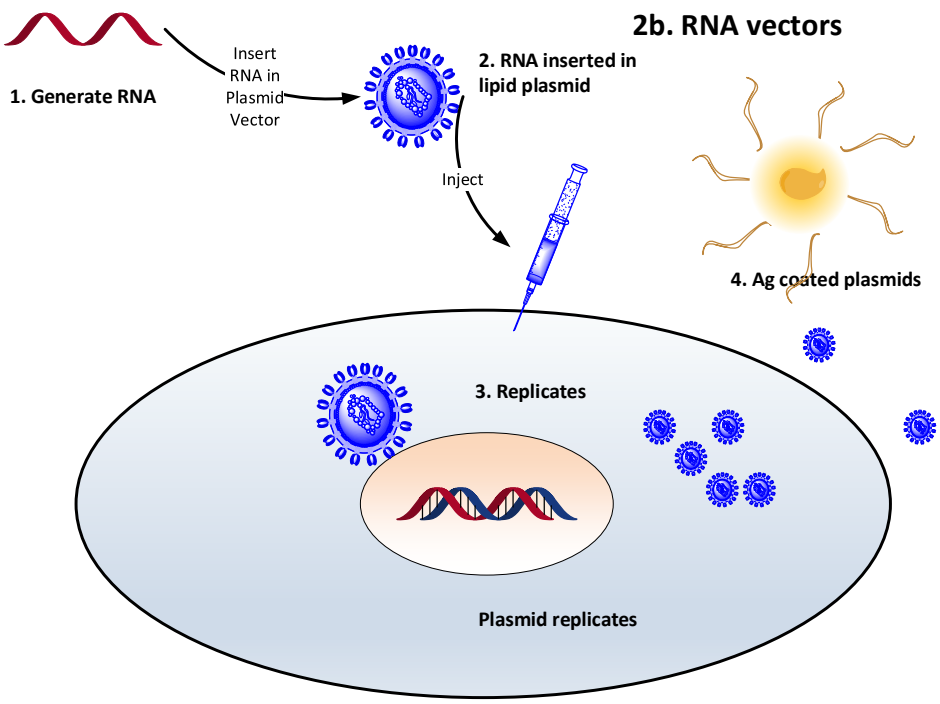
A second way is a DNA vector injected into a patient and we use an electric shock to open the cell surface.



Needless to say this has advantages and disadvantages. Trying to get DNA into a cell is much more complex than RNA. DNA is not as flexible and thus the shock requirement.

5.3 RNA VECTOR

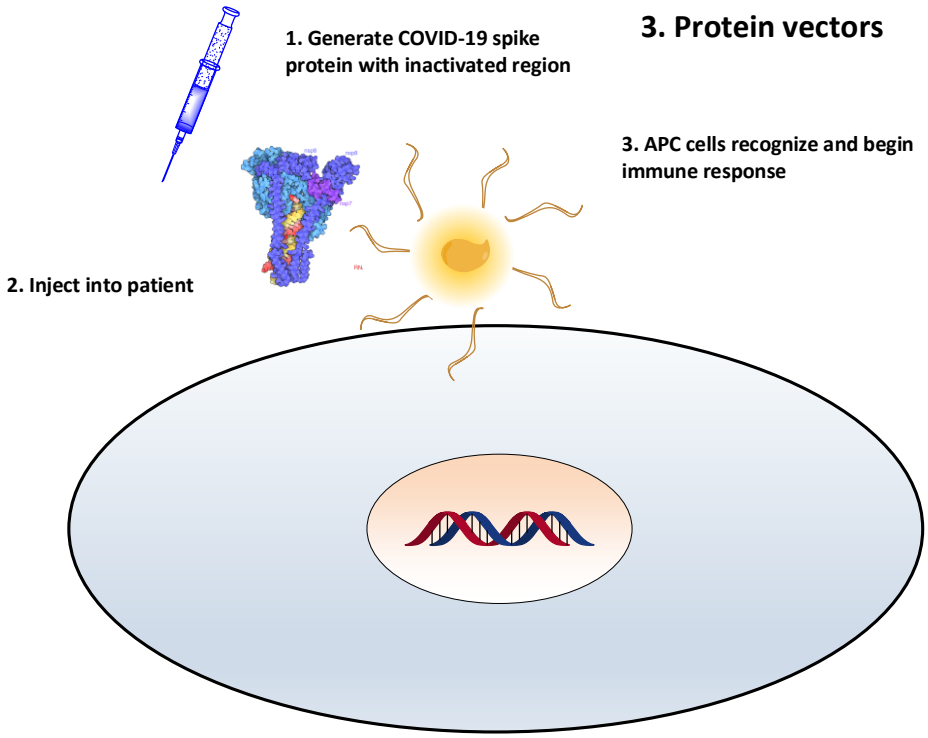
We can also use RNA to generate the Ag via a normal vaccination. Both of these are highly scalable and no eggs required. The MRNA approach we shall discuss at length in the next section. Simple the MRNA is generated, then placed in a lipid polysaccharide shell, injected, and the LPS mRNA complex get taken up by the cell producing the spike which the APCs and the immune system respond to. Since this mRNA produces only the spike protein as we noted earlier it presents minimal secondary concerns.



This approach seems to be the most favored also due to the ease of production. However distribution can be complex due to stability issue related to the LPS nano spheres.

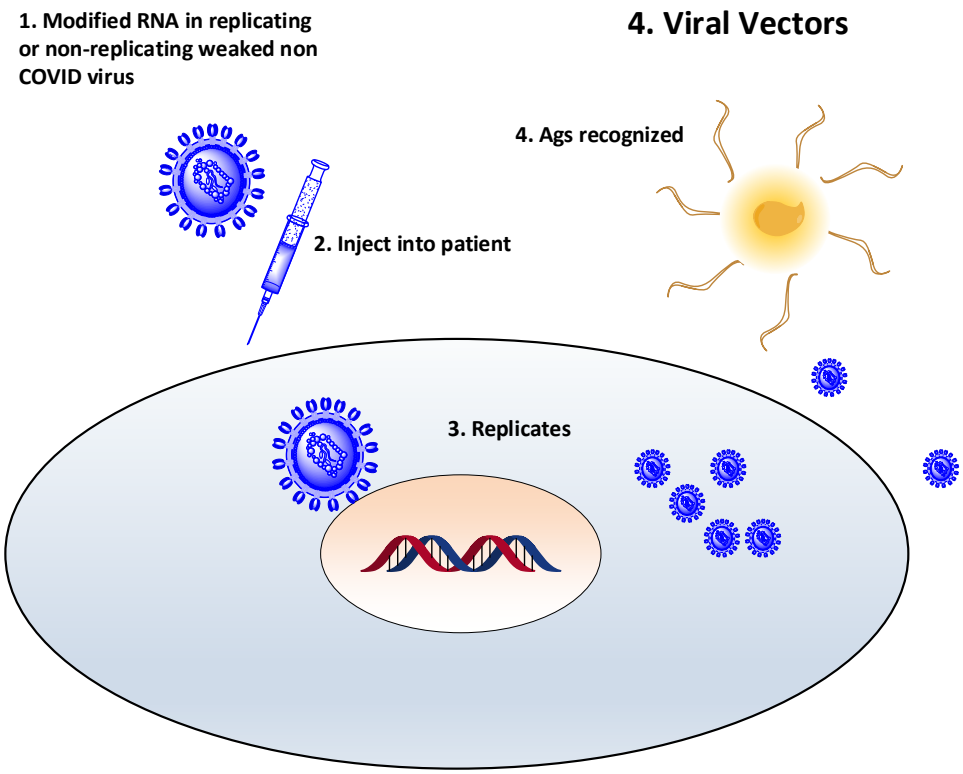
5.4 PROTEIN VECTORS

Another way is a protein vector such as the COVID protein but with segments deleted.



5.5 VIRAL VECTOR

Finally, there is a viral vector where we use the deactivated protein but place it in a more benign virus. We have used viral vectors in a variety of other approaches especially for certain cancer treatments.



Just which of these will win out is unknown.

5.6 Recent Status

A significant amount of effort along multiple lines has been directed at vaccine development. From the paper by Alter et al we have the following list as of October 2020:

Sponsor	Vaccine type (product)	Clinical stage
Beijing Institute of Biological Products, Sinopharm	Inactivated virus	Phase 3
Wuhan Institute of Biological Products, Sinopharm	Inactivated virus	Phase 3
Sinovac Biotech. Instituto Butantan, Bio Farma	Inactivated virus (inactivated SARS-CoV‑2 plus alum; Corona Vac; formerly PiCoVacc)	Phase 3
University of Oxford. Oxford Biomedica. Vaccines Manufacturing and Innovation Centre, Pall Life Sciences. Cobra Biologies, Halix. Advent, Merck, Serum Institute of India. Vaccitech, Catalent, AstraZeneca, IQVIA	Non-replicating viral vector (chimpanzee adenoviral vector encoding S protein; AZD1222; formerly ChAdOxI)	Phase 3
Moderna. NIAID, Lonza, Rovi. Medidata, Bioqual	RNA-based (nucleoside-modified mRNA vaccine encoding codon-modified S protein encapsulated in ionizable LNPs, containing distearoyl phosphatidylcholine, cholesterol and polyethylene glycol lipid)	Phase 3
Gamaleya Research Institute of Epidemiology and Microbiology	Ad5 and Ad26 with a coronavirus gene, administered separately	Phase 3
CanSino Biologies, Beijing Institute of Biotechnology, National Research Council of Canada	Non-replicating viral vector (AdS vector encoding S protein)	Phase 3
BioNTech, Fosun Pharma, Pfizer	RNA-based (mRNA vaccine expressing codon-optimized, nucleoside-modified mRNA that encodes trimerized RBD in ionizable cationic LNPs containing phosphatidylcholine, cholesterol, polyethylene glycol lipid)	Phase 2/3
Institute of Medical Biology. Chinese Academy of Medical Sciences	Inactivated virus	Phase 2
Anhui Zhifei Longcom Biopharmaceutical; Institute of Microbiology, Chinese Academy of Sciences	Protein subunit (adjuvanted recombinant protein RBD dimer)	Phase 2
CureVac	Protamine-complexed mRNA vaccine expressing undisclosed SARS-CoV‑2 protein	Phase 2
Zydus Cadila	Electroporated DNA vaccine encoding undisclosed SARS-CoV-2 protein	Phase 2

At this time, no one of the above has received approval. Note that just two are mRNA vaccines and that more classic vaccine approaches are also present.

Tregoning et al present a Table as shown below (as modified) giving the advantages and disadvantages of these methods.

Vaccine	*Advantage*	*Disadvantage*
Live Attenuated	Good track record Manufacturing capacity	Risk of reversion to pathogenic form Slow to develop new versions Risk of infection in immunocompromised patients May require BSLIII to generate and test
Inactivated vaccines	Fast to generate Long track record	Need live virus and facility to grow large amounts Risk of vaccine-enhanced disease
Protein vaccines	Safe	Potentially poorly immunogenic without adjuvant
Including VLP	Very common platform	Risk of wrong conformation Slow and more expensive manufacture
Peptide	T cell response	Risk of T cell enhanced disease Poorly immunogenic
aAPC	T cell response	Requires cell manufacture, issues of scale up Impractical
Viral vectored vaccines	No need to grow live virus Fast to generate Safe track record	Pre-existing anti-vector immunity T cell focused response, lower antibody induction Requires low temperature (-80°C) storage Replicating vectors not suitable for immunocompromised patients
DNA vaccines	Fast to generate Safe Thermostable	Poor track record of immunogenicity in human trials
mRNA vaccines	Fast to generate Translation in cytosol. Recent efficacy Phase III Trial is positive.	Unstable Needs formulation. Demands low temperature storage.
saRNA vaccines	Fast to generate Requires lower dose than mRNA Potential for mass production	New platform: Previously not been in human clinical trial Unstable Needs formulation

This is a reasonable and current Table for comparison.

6 MRNA VACCINE DETAILS

We now will focus on the mRNA vaccine since it has significant advantages of insertion and production. However, as Pfizer has noted it demands extreme storage requirements at approximately -100F [10], [11]. Although this is not liquid nitrogen levels it does add a level of complexity. As Maruggi et al have noted:

In the last two decades, there has been growing interest in mRNA-based technology for the development of prophylactic vaccines against infectious diseases. Technological advancements in RNA biology, chemistry, stability, and delivery systems have accelerated the development of fully synthetic mRNA vaccines.

Potent, long-lasting, and safe immune responses observed in animal models, as well as encouraging data from early human clinical trials, make mRNA-based vaccination an attractive alternative to conventional vaccine approaches. Thanks to these data, together with the potential for generic, low-cost manufacturing processes and the completely synthetic nature, the prospects for mRNA vaccines are very promising. In addition, mRNA vaccines have the potential to streamline vaccine discovery and development, and facilitate a rapid response to emerging infectious diseases.

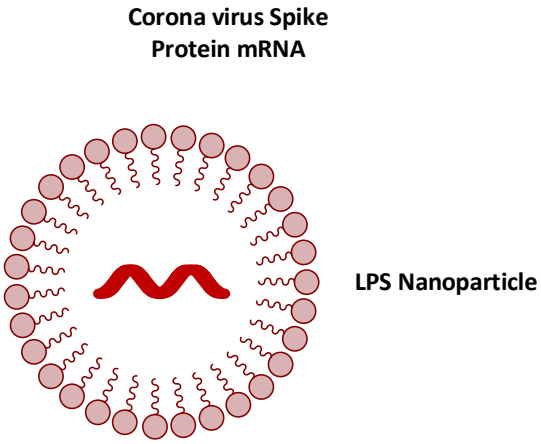
In this review, we overview the unique attributes of mRNA vaccine approaches, review the data of mRNA vaccines against infectious diseases, discuss the current challenges, and highlight perspectives about the future of this promising technology

6.1 PRINCIPLES

As we noted earlier the mRNA vaccine is a lipid polysaccharide nano shell with the mRNA of the spike protein contained therein. The goal is to get the nano particle into the body, then the mRNA into the cells, read and translate the mRNA to generate the spike protein. Then the spike protein is expressed and can be used as an antigen to start the adaptive immune process.

[10] https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-vaccine-candidate-against

[11] https://www.reuters.com/article/health-coronavirus-vaccines-distribution/why-pfizers-ultra-cold-covid-19-vaccine-will-not-be-at-the-local-pharmacy-any-time-soon-idUSKBN27P2VP



We demonstrate this process below. Namely this is a way to start the process going since we know the sequence of the virus that generates the spike at the DNA level and we thus know the mRNA segment. We have shown that earlier when examining the virus.

As Maruggi et al note there are two classifications:

Conventional mRNA Vaccines*: A conventional mRNA vaccine carries only the coding sequence of the antigen of interest flanked by regulatory regions. The major advantages of the conventional mRNA vaccine approach are the simplicity and relatively small size of the RNA molecule. In the simplest form, the stability and activity of the conventional mRNA in vivo is limited, because of propensity of cells to limit duration of expression. However, optimization of RNA structural elements and formulation can increase antigen expression and durability.*

Self-Amplifying mRNA Vaccines: *Self-amplifying mRNA vaccines are commonly based on the engineered RNA genome of positive-sense single-stranded RNA viruses, such as alphaviruses, flaviviruses, and picornaviruses. In all cases, the mRNA mimics the replicative features of positive-sense singlestranded RNA viruses with the goal of increasing the duration and magnitude of the expression, as well as subsequent immunogenicity of the encoded antigen. The best-studied self-amplified mRNA molecules are derived from alphavirus genomes, such as those of the Sindbis virus (SINV), Semliki Forest virus (SFV), and Venezuelan equine encephalitis viruses (VEEVs). Negative-sense single-stranded RNA viruses, such as rhabdoviruses and measles viruses, can also be utilized for the development of RNA-based vaccines*

As Zhang et al have noted regarding liquid nanoparticles which were thermostable[12]. They note:

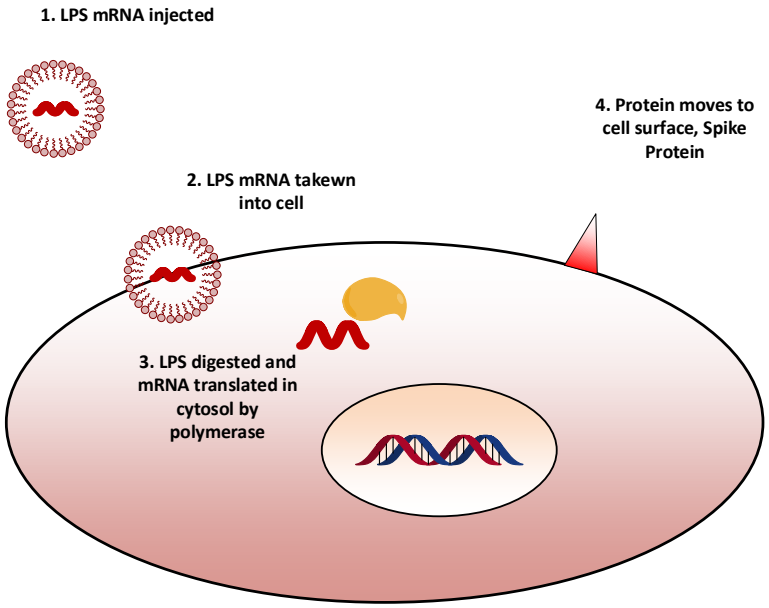
Lipid nanoparticles (LNPs) are one of the most appealing and commonly used mRNA delivery tools. Here we developed a vaccine platform based on modified mRNA encapsulated in LNPs for

[12] Zhang et al define thermostable as follows: *FLuc mRNA-LNP was incubated at 4, 25 or 37C for 1, 4, and 7 days.* This means that unlike the Moderna and Pfizer vaccines which need storage at -100F this is putatively more useful.

in vivo delivery. The RBD of SARS-CoV-2 was chosen as the target antigen for the mRNA coding sequence…

Transfection of the RBD-encoding mRNA in multiple cell lines resulted in high expression of recombinant RBD in culture supernatants, with up to 917.4 ng/mL of RBD in mRNA-transfected HEK293F cells. RBD protein expressed from mRNA retained high affinity for recombinant human ACE2, as demonstrated by kinetics analysis using ForteBio Octet, and functionally inhibited entry of a vesicular stomatitis virus (VSV)- based pseudovirus expressing the SARS-CoV-2 S protein in Huh7 cells. Immunostaining further demonstrated that this RBD protein can be recognized by a panel of monoclonal antibodies (mAbs) against SARS-CoV-2 RBD as well as convalescent sera from three COVID-19 patients.

The mRNA-LNP formulations were prepared using a modified procedure, as described previously for small interfering RNA (siRNA), followed by tangential flow filtration and purification before being filled into sterile glass vials. The characterization of representative batches of mRNA-LNP. The final stock of SARSCoV-2 RBD encoding mRNA-LNP (ARCoV), manufactured under good manufacturing practice (GMP) conditions, showed an average particle size of 88.85 nm with more than 95% encapsulation…..

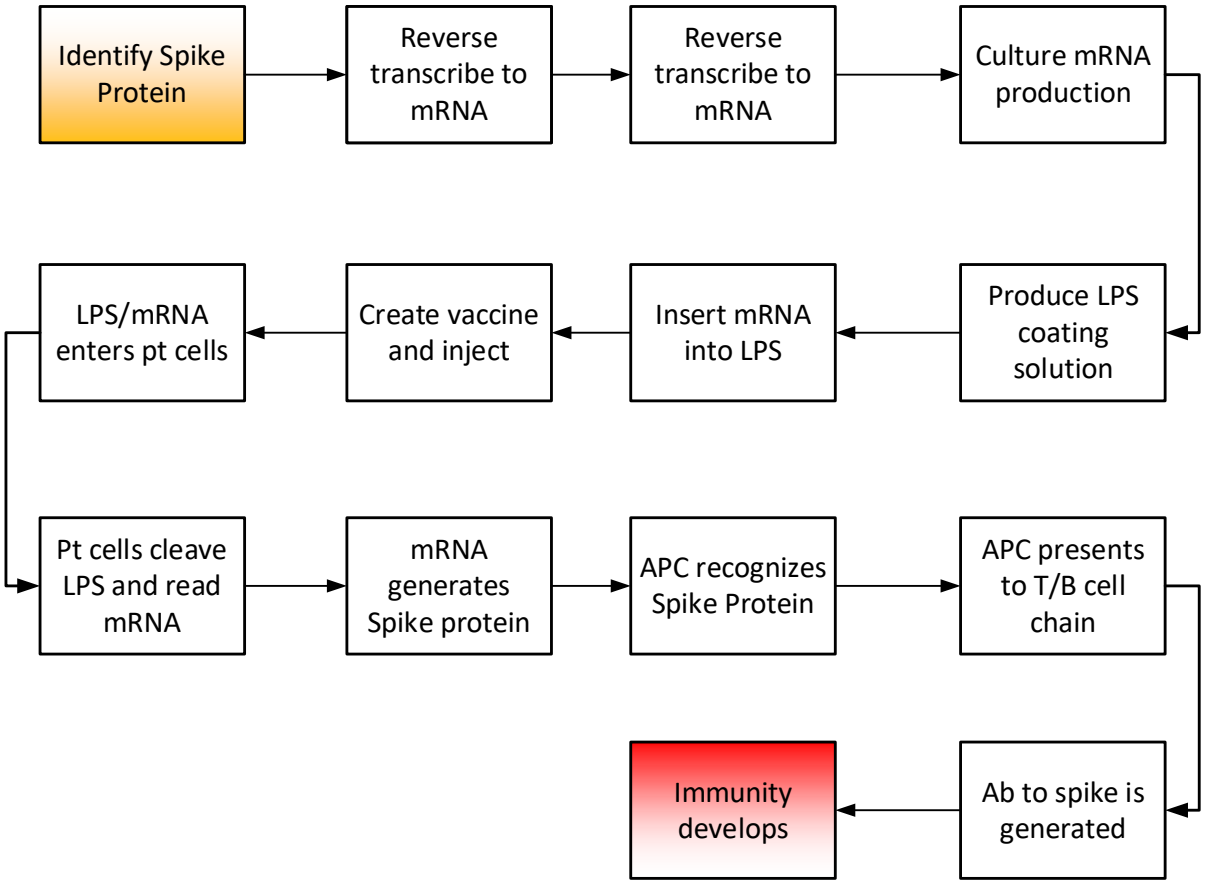


The principle is relatively simple. The challenge is always production and scale, and of course costs.

6.2 PRODUCTION

Now the question is how does one develop and produce the vaccine. The following is a possible path. It starts with the assumption that the spike protein is the reasonable Ag target, then starts

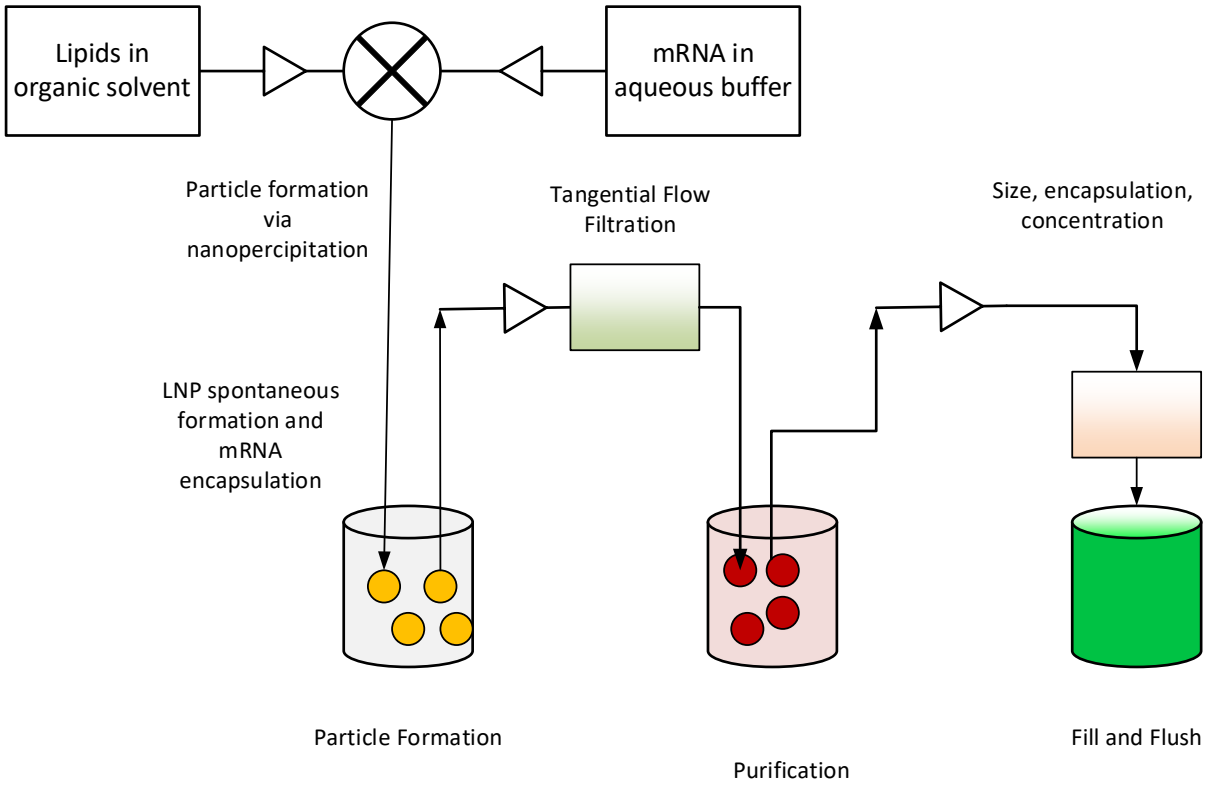
the process of isolating the mRNA segment, reproducing it and then using a lipopolysaccharide as a transport mechanism.



We have to assume that this Ag mechanism results in an Ab response. Even if it does it must have some lasting response, not just a short term one. Now the production process for mRNA vaccines is shown below based upon Zhang et al. One can also look at Prager for more details regarding standards and FDA/EMA requirements. Zhang et al note:

ARCoV is manufactured through rapid mixing of mRNA in aqueous solution and a mixture of lipids in ethanol. This process yields self-assembled LNPs with mRNA encapsulated inside. Tangential flow filtration was used to remove ethanol and to concentrate the solution. Following the Quality Control (QC) procedure, the final product was filtered into sterilized glass syringes or glass vials.

Namely one takes the mRNA which has been separately produced and combine it with the LPS which is in a liquid organic solvent. We use PEG (polyethylene glycol) for many of our processes. Then there is a filtration, titration by size, and the product is available.



The mRNA production is as follows by Zhang et al:

The mRNA was produced in vitro using T7 RNA polymerase-mediated transcription from a linearized DNA template from plasmid ABOP-028 (GENEWIZ), which encodes codon-optimized RBD region of SARS-CoV-2 (Figure S1) and incorporates the 50 and 30 untranslated regions and a poly-A tail. The FLuc-encoding mRNA (FLuc-mRNA) was prepared from plasmid ABOP-010 (GENWIZ) in the same procedure

In a sense, if we have the RNA sequence we can generate the underlying DNA via reverse transcriptase. Then using PCR we can multiply the DNA and then with this large batch reproduce the mRNA using standard transcription techniques. Scaling this process may be complex but it is doable. Furthermore throughout we must ensure high quality checking in the process. Again this is akin to the many monoclonal Ab products on the market. Ahammad and Lira indicate this process in some detail.

LPS encapsulation as follows:

Lipid-nanoparticle (LNP) formulations were prepared using a modified procedure of a method previously described for siRNA. Briefly, lipids were dissolved in ethanol containing an ionizable lipid, 1, 2-distearoyl-sn-glycero- 3-phosphocholine (DSPC), cholesterol and PEG-lipid (with molar ratios of 50:10:38.5:1.5). The lipid mixture was combined with 20 mM citrate buffer (pH4.0) containing mRNA at a ratio of 1:2 through a T-mixer. Formulations were then

diafiltrated against 10 3 volume of PBS (pH7.4) through a tangential-flow filtration (TFF) membrane with 100 kD molecular weight cut-offs , and concentrated to desired concentrations, passed through a 0.22 mm filter, and stored until use. All formulations were tested for particle size, distribution, RNA concentration and encapsulation.

Overall the process demands ongoing and complex quality controls. The mRNA production yields are unknown based upon the information presented but one can assume that a reasonable ramping up can be obtained. We have examined mAb production and many of the same production environment can be used.

6.3 EXECUTION

The next step would entail the delivery of the vaccine and its direct patient application. As Shin et al have noted:

The rapid emergence of the COVID-19 pandemic has also raised concerns regarding critical deficiencies in manufacturing and distribution of vaccines. Even when an effective vaccine is developed, considerations of cost, formulation and scale-up manufacturing must be taken into account. … it is critical to also consider technologies and platforms suited for developing countries. Recombinant protein production can be carried out in a variety of platforms, each coming with its own advantages and disadvantages regarding yields, regulatory compliance, cost, scalability, flexibility, speed and safety.

While traditional manufacturing processes using bioreactors and mammalian, bacterial or yeast cell cultures are well-established in the pharmaceutical sector, these platforms are expensive, and production can be hampered by human pathogen contamination. Innovative manufacturing technologies that can meet the required global demand and distribution in response to outbreak have recently been deployed with success.

Plant-based expression systems have emerged in the past decade and already made an appearance during the 2014 Ebola epidemic when patients were treated with ZMapp, an antibody cocktail manufactured through molecular farming. Plant molecular farming approaches offer scalability: while in fermentation-based platform, every scale-up step needs to be carefully verified—in molecular farming, each plant is a bioreactor.

The more plants are grown, the more product is made; scale-up does not change the upstream production processes. Other positive attributes of the molecular farming platform are the low manufacturing costs, the inability of human pathogens to replicate in plant cells (hence safety), and relatively non-sophisticated infrastructure that could be implemented worldwide also in low-resource countries.

As Maruggi et al note regarding the pros and cons:

Vaccines	*Advantages*	*Disadvantages*
Conventional mRNA Self-amplifying mRNA	1. synthetic production; egg and cell free 2. rapid and scalable production compared with other vaccine platforms (e.g.・ subunit proteins, viral vectors) 3. noninfectious, non-integrating, and naturally degraded 4. expression in situ to produce antigens with structure unaltered by in vitro manufacturing process 5. expression in situ to stimulate innate immune response, enhancing broad T and B cell immune responses	1. concerns with instability 2. limited immunogenicity data in humans 3. potential toxic elect of free extracellular RNA 4. inflammation due to enhanced type we IFN activation 5. efficient deliver)' required to deliver and launch self-amplifying mRNA 6. efficient deliver)' required to deliver and/or provide adjuvating effect for conventional mRNA 7. unproven toxicity profiles of deliver)' system components
Conventional mRNA	1. shorter RNA length compared with self-amplifying mRNA 2. applicable to nucleoside base modification 3. direct antigen expression from mRNA 4. no risk of anti-vector immunity	1. potential toxicity from modified nucleotides 2. shorter duration of expression 3. higher effective RNA doses
Self-amplifying mRNA	1. enhanced and prolonged antigen expression 2. lower effective RNA doses, potentially resulting in better safety 3. intrinsic adjuvant effect 4. potential apoptosis of vaccine-carrying cells due to vaccine self-amplification, leading to enhanced cross-presentation 5. option for single-vector delivery of multiple or complex antigens	1. potential elevated inflammation due to self-amplification 2. longer RNA length, may lead to more challenging production of high-quality RNA compared with conventional mRNA 3. interaction between nsPs and host factors yet to be addressed

7 OBSERVATIONS

By examining the actual details of the viral spread and understanding the virus control, then looking at the vaccine approaches we can make a significant number of observations. Many of these build on what we have noted since the beginning of this pandemic.

7.1 POLY-SPECIFIC NANOBODIES

Bi-specific Ab have been developed for multiple applications. Unlike monoclonal Ab, which are typical Ab but targets at a specific Ag, Poly-specific Ab, nanobodies, are targeted at multiple Ag or receptor sites. Dong et al have presented a significant result in this area. They note:

SARS-CoV-2 is a newly emergent coronavirus, which has adversely impacted human health and has led to the COVID-19 pandemic. There is an unmet need to develop therapies against SARS-CoV-2 due to its severity and lack of treatment options. A promising approach to combat COVID-19 is through the neutralization of SARS-CoV-2 by therapeutic antibodies.

Previously, we described a strategy to rapidly identify and generate llama nanobodies (VHH) from naïve and synthetic humanized VHH phage libraries that specifically bind the S1 SARS-CoV-2 spike protein, and block the interaction with the human ACE2 receptor. In this study we used computer-aided design to construct multi-specific VHH antibodies fused to human IgG1 Fc domains based on the epitope predictions for leading VHHs.

The resulting tri-specific VHH-Fc antibodies show more potent S1 binding, S1/ACE2 blocking, and SARS-CoV-2 pseudovirus neutralization than the bi-specific VHH-Fcs or combination of individual monoclonal VHH-Fcs. Furthermore, protein stability analysis of the VHH-Fcs shows favorable developability features, which enable them to be quickly and successfully developed into therapeutics against COVID-19.

We believe that poly-specific Ab have significant potential both as a vaccine adjuvant and as therapeutic carrier in addition to activating an immune response.

7.2 MASKS VS NO MASKS

We have been told that masks will prevent us from getting infected. In fact, the head of the CDC even told Congress that a mask is better than a vaccine. In a September NEJM article the authors state[13]:

One important reason for population-wide facial masking became apparent in March, when reports started to circulate describing the high rates of SARS-CoV-2 viral shedding from the noses and mouths of patients who were presymptomatic or asymptomatic — shedding rates

[13] https://www.nejm.org/doi/full/10.1056/NEJMp2026913

equivalent to those among symptomatic patients. Universal facial masking seemed to be a possible way to prevent transmission from asymptomatic infected people. The Centers for Disease Control and Prevention (CDC) therefore recommended on April 3 that the public wear cloth face coverings in areas with high rates of community transmission — a recommendation that has been unevenly followed across the United States....

To test our hypothesis that population-wide masking is one of those strategies, we need further studies comparing the rate of asymptomatic infection in areas with and areas without universal masking. To test the variolation hypothesis, we will need more studies comparing the strength and durability of SARS-CoV-2–specific T-cell immunity between people with asymptomatic infection and those with symptomatic infection, as well as a demonstration of the natural slowing of SARS-CoV-2 spread in areas with a high proportion of asymptomatic infections. Ultimately, combating the pandemic will involve driving down both transmission rates and severity of disease. Increasing evidence suggests that population-wide facial masking might benefit both components of the response.

Now several respondents in NEJM note the opposite[14]:

We caution against incorporating hypotheses about masks functioning as effective "variolation" …into public health messaging without considering the implications and nuances. The term "variolation" should be avoided because it is inaccurate with respect to coronaviruses, and it describes an obsolete and risky practice that was used for the iatrogenic inoculation of smallpox. There is insufficient evidence to support the claim that masks reduce the infectious dose of SARS-CoV-2 and the severity of Covid-19, much less that their use can induce protective immunity. Substantial knowledge gaps must be addressed before claims are made about the efficacy of face masks in reducing morbidity or eliciting immune responses.

Masks are used primarily to reduce SARS-CoV-2 transmission rather than reduce the dose of infectious particles or mitigate the severity of Covid-19. The suggestion that masks offer an alternative to vaccination without evidence that the benefits outweigh the great risks implicitly encourages reckless behavior. With the lack of a vaccine, nonpharmaceutical interventions continue to be the best preventive tools. Transparent, contextualized messaging and embracing uncertainty are essential while science moves forward. Currently, there are too many research gaps to conclude that masks offer benefits beyond reducing transmission risk. We should not advocate for these benefits without fully comprehending the risks.

This back and forth lacks fundamental reliable data. The latter states that masks may work preventing an infected person infecting others. Whereas the former seems to rely upon masks no matter what. Despite the Politicians relying on Science, science by its very nature is Hegelian, thesis, antithesis, synthesis. And then we start all over again. The paradigm of mask wearing has clearly become a political statement. It is the Tricolore of the Jacobins, wear it or get beheaded.

[14] https://www.nejm.org/doi/full/10.1056/NEJMc2030886?query=RP

It would be worthwhile to have some reasonable studies. Not academic one offs, such as photographing a sneeze. Aerosols are real, but they are also quite complex. Newtons laws fundamentally apply, assuming we can account for all the forces, downward and upward. Thus, if an aerosol contains warm air from the lungs of an infected person, in the winter the warm air is much less dense than the cold and thus this particle "floats" on the denser cold air. Archimedes knew this in his bathtub on Sicily millennia ago. Our "scientists" seem clueless regarding this, at least for publishing results.

Thus, should we wear a mask? Like Descartes and others, it is akin to believing in God, what do you have to lose.

7.3 IMMUNIZATION STRATEGIES

When asked recently the Governor of New Jersey fumbled his articulation of the State plan, if there is one, for distribution of immunizations. The CDC put out a plan but the plan has many gaps needing completion. For example:

1. Phasing: There is essentially three phases. Phase 1 is critical workers such as physicians, nurses, Fire and Police, LTC staff and residents. Phase 2 is possible at risk such as those over 65 but relatively healthy, teachers, and those required for general economic welfare. Phase 3 is everyone else.

2. Distribution: How does the vaccine get from the manufacturer to a point of delivery?

3. Points of Delivery: Where and how do we deliver the vaccine to people. If we had a good Public Health system we could have used that for all Phase 1. Phase 2 and 3 could access it as we do now with flu shots; local drug stores.

4. Scheduling: How do we schedule the people? Phase 1 seems simple if and only if we had Public Health folks. Phases 2 and 3 can be done by Internet scheduling as is done with flu shots. However one must beware of baseless assumptions like everyone having and understanding Internet access.

5. Tracking: Since the corona virus has limited immunity we must be certain we drive infections to zero meaning annual immunizations. It also means testing. Thus, despite the concerns, we should photo each patient and give them an identity card showing what and when they were vaccinated. we had mine from 1949! Still do. Then this can be used possibly for travel, domestic and international.

6. Testing: Testing must continue unabated. That means massive random tests and not the type today. Percent positives are totally meaningless unless we randomly test a very large sample.

7.4 HERD IMMUNITY

The NIH has published a piece reflecting the possible leak of long term immunity to COVID-19 infections. They note:

The new findings show that people who survive a COVID-19 infection continue to produce protective antibodies against key parts of the virus for at least three to four months after developing their first symptoms. In contrast, some other antibody types decline more quickly. The findings offer hope that people infected with the virus will have some lasting antibody protection against re-infection, though for how long still remains to be determined. In one of the two studies, partly funded by NIH, researchers led by Richelle Charles, Massachusetts General Hospital, Boston, sought a more detailed understanding of antibody responses following infection with SARS-CoV-2. To get a closer look, they enrolled 343 patients, most of whom had severe COVID-19 requiring hospitalization.

They examined their antibody responses for up to 122 days after symptoms developed and compared them to antibodies in more than 1,500 blood samples collected before the pandemic began. The researchers characterized the development of three types of antibodies in the blood samples.

The first type was immunoglobulin G (IgG), which has the potential to confer sustained immunity.

The second type was immunoglobulin A (IgA), which protects against infection on the body's mucosal surfaces, such as those found in the respiratory and gastrointestinal tracts, and are found in high levels in tears, mucus, and other bodily secretions. The third type is immunoglobulin M (IgM), which the body produces first when fighting an infection.

In the limited data on patients we have seen it appears that some form of immunity may exist for several months but that the Ab do drop significantly. If that means loss of any immunity then what we have is a disease that requires annual, at the very least, re-immunization.

Herd immunity does not exist in the classic sense. Simply, reinfection is possible and we have seen that already. However the reinfections are often with "mutated" virus RNA. One could assume that the elegantly engineered corona virus may have been designed that way but that would be mere speculation.

Notwithstanding, any suggestion that we rely upon herd immunity is not only specious but harmful and wrong. It is worth reading the reference papers in the above article to see just this effect.

7.5 POLITICS

Both Nature15[1] and Science16[2] have come out to support the Democrat and to be repulsed by the Republican. Not having a horse in this race, we felt it was worth commenting upon the now grossly political nature of these long-time bastions of scientific facts. we have noticed since the Vietnam days that these organs have slowly morphed into political and policy documents which from time to time present compelling scientific insights. Let me address just a few issues; Science states:

At home, Biden says he'll work with governors and local officials to encourage greater use of physical distancing and masks—possibly even mandating their use at federal facilities and on federal lands. And he's vowed to reverse the erosion of public trust in two key health agencies, the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA), by appointing new leadership and improving the transparency of decision-making.

Let us examine the facts. The CDC lost public trust because of its own gross incompetence. As we have noted before on multiple occasions, we publicly knew the pandemic was upon us on January 29th with the publication in NEJM of the articles detailing the Wuhan epidemic. That was the clanging bell. Ironically from January 16 through February 6 the White House was engaged in the House initiated impeachment trial. Needless to say, a distraction but it should not have distracted the CDC. One must remember that most of the "leadership" of the CDC was a remnant of the previous administration. As to the FDA, is has a long reputation of being glacial in its movements, and often for good reason.

Universities and Spending: The driver one suspects for this support is the promised increase in University support. Specifically, they note:

Keeping the economy afloat through the pandemic will require massive federal spending, Biden says, and he will likely ask lawmakers to approve a host of spending initiatives early in his term. Universities and research groups want some of the money, saying federal science agencies need tens of billions of dollars to help them recover from the pandemic.

However, one wonders what Universities have done to merit such support. In World War II, MIT and U Cal, Columbia, U Chicago and many others banded together to develop radar, weapons, and other strategic elements that allowed us to overcome the monsters who were destroying mankind. Since Vietnam, universities want money but seem to think there is no obligation to assist the nation. Where was the Rad Lab equivalent at MIT? Nowhere, in fact there was blatant opposition to anything supporting the effort to overcome the viral attack.

In contrast, it appears that we have great strides in therapeutics and vaccines, all from private industry. In this war against COVID, industry has stepped up with massive Government funding and most likely will deliver a vaccine early next year. Consider what Government has not done,

---

15[1] https://www.nature.com/articles/d41586-020-02852-x

15[2] https://www.sciencemag.org/news/2020/10/biden-presidency-could-have-remarkable-impact-science-policy-also-face-hurdles

no Ebola or AIDS vaccine. After billions of Government spending, and decades of AIDS effort, NIAID has delivered nearly nothing in AIDS and limited amounts in Ebola and other pandemic viral infections.

Government Workers: One must remember that there are millions of such workers. High Tech has siphoned off many highly competent people as has industry. The Government gets what is left.

Under Trump, many researchers who work for the federal government have said they don't feel valued or respected. Employee surveys show job satisfaction at several science agencies has taken a nosedive, and there have been many anecdotal reports of researchers leaving their jobs. Biden says he wants to reverse that trend, starting by replacing Trump appointees who have suspect scientific credentials or hold views far out of the mainstream. "The house cleaning could be remarkable; in some cases you are going to see hacks who are flat-out science deniers replaced by appointees who not only understand the science, but have done it themselves," says one lobbyist who requested anonymity because he still interacts with the Trump administration.

Government workers for the most part act as intermediaries. NIH does fundamental research but it also acts as an administrative organ managing external research funding. The "hacks" that the writer notes have always been with us. we have seen first-hand in the Carter Administrations many such hacks. Go from one administration to another and the cast of characters may change but the characteristics do not. The "Plum Book" is an example of the list of the many favored positions given to supporters and their related friends. Our Government has always been populated at the high levels by political types.

Overall, the reasons noted have multiple facets. There is no clear path, some good and some not so good. Yet scientists must learn that this is the essence of politics…perhaps why Washington gave them a swamp for the Capitol.

7.6 EXECUTION

In reviewing the CDC "proposal" for management and implementation of the vaccination program they note:

An adequate network of trained, technically competent COVID-19 vaccination providers in accessible settings is critical to COVID-19 Vaccination Program success. For this reason, COVID-19 vaccination provider recruitment and enrollment may be the most critical activity conducted before vaccine becomes available. Jurisdictions and tribal organizations should concentrate early planning efforts on engaging those vaccination providers and services that can rapidly vaccinate initial populations of focus as soon as a COVID-19 vaccine is available (Phase 1).

Subsequent planning should include measures for recruiting and enrolling enough providers to vaccinate additional critical populations and eventually the general population when sufficient vaccine supply is available (Phases 2 and 3).

Vaccination Provider Recruitment Jurisdictions are encouraged to immediately reach out to potential COVID-19 vaccination providers and target the appropriate settings so that COVID-19 vaccination services are accessible to the initial populations of focus when the first COVID-19 vaccine doses arrive. Providers and settings that maximize the number of people who can be vaccinated should be prioritized for enrollment; however, jurisdictions should ensure social distancing and other infection control procedures can be maintained in selected settings (see CDC guidance on vaccination during a pandemic).

All providers/settings, especially those enrolled for Phase 1, must able to meet the reporting requirements discussed in Section 9: COVID-19 Vaccine Administration Documentation and Reporting and Section 11: COVID-19 Requirements for Immunization Information Systems or

Other External Systems. Jurisdictions should consider partnering with the private sector and with local hospitals or health systems to provide COVID-19 vaccination in the closest proximity possible to the initial populations of focus. For example, partnering with critical access hospitals will be key to vaccinating Phase 1 populations in rural areas. Suggested early COVID-19 vaccination providers/settings include:

• Large hospitals and health systems
• Commercial partners (e.g., pharmacies)
• Mobile vaccination providers
• Occupational health settings for large employers
• Critical access hospitals, RHCs, community health centers, or other central locations that can provide vaccination services for a broad area

CDC is working to engage large pharmacy partners to assist with on-site vaccination in LTCFs. These partners have existing distribution and administration infrastructure (including cold chain) and relationships with some LTCFs to provide medication and, in some cases, vaccination services (e.g., seasonal influenza) for staff and residents in LTCFs; this may reduce burden on jurisdictional health departments.

CDC will ensure jurisdictions have visibility on this work with large pharmacy partners. Jurisdictions should recruit additional COVID-19 vaccination providers to expand equitable access to COVID-19 vaccination when vaccine supply increases. Enrollment activities should be tracked so vaccination providers are not approached multiple times.

Unfortunately this is a general statement lacking specificity. The last sentence is the most critical. It leaves the details to the jurisdictions, we assume States. Unfortunately we saw how well this worked. But fundamentally the CDC is ill equipped to manage this effort. As they say, the devil is in the details.

Then there is the Emanuel et al plan, the "Fair Priority Model", from the person who gave us the "Death Panels" under Obamacare. They note:

Fairly distributing a COVID-19 vaccine among countries is a problem of distributive justice. Although governments will be the initial recipients of vaccine, fair distribution across countries

must reflect a moral concern for the ultimate recipients: individuals. Three values are particularly relevant : benefiting people and limiting harm, prioritizing the disadvantaged, and equal moral concern.

Benefiting people and limiting harm is widely recognized as important across ethical theories. Realizing this value requires defining relevant benefits, measuring them, and assessing the relative urgency—the importance and time sensitivity—of countries' needs. A successful vaccine produces direct benefits by protecting people against death and morbidity caused by infection. It also produces indirect benefits by reducing death and morbidity arising from health systems overstressed by the pandemic, and by reducing poverty and social hardship such as closed schools …

The Fair Priority Model is the best embodiment of the ethical values of limiting harms, benefiting the disadvantaged, and recognizing equal concern. The responsibility for implementing the model rests with countries, international organizations, and vaccine producers.

Fundamentally their "ethics", based upon what we do not know, relegates the distribution in such a manner to those the Government deems useful, oftentimes voters for their remaining in office and on the dole. These folks base their life and death decisions on their own personal value system. The "people be damned" is generally the approach. It is classic Progressive mindset that states individuals do not count only the wisdom of the self-selected few.

7.7 EXPERTS VS AMATEURS

What is an expert and what is an amateur? Is the expert better than the amateur? Are experts credible? Who decides who is an expert? Can an amateur be reliable when opining on a topic?

In the midst of this COVID pandemic we have a limited number of experts and a massive number of amateurs. Should we trust the experts? One need look no farther that the London group and the University of Washington group. All predicted massive death counts, London in the millions, and here we sit with a count less than a flu outbreak and an economy in free fall. Yet the powers to be select their chosen experts and follow the "science"

However, science is a truly combative field. A group may present a result and a conclusion and no sooner do we get some other group refuting that with more data. Retractions run rampant in our professional literature and reproducible results are all too often far and few between. Thus, should we trust these experts without question?

Let us briefly examine some definitions.

What is an expert and what is an amateur? Generally, an expert is someone who is paid by a third party to perform certain actions, such as teaching, law, medicine, science, based upon their training and acceptance by the paying party. There are Expert Witnesses at trials, and the law is quite clear on who can be an expert. In the US system such experts are confronted by the opposing party and testify at trial and are cross examined. These Expert Witnesses can face a

brutal examination of their training, bona fides, personal lives and whatever the other side may use to impeach their opinions. Academic experts on the otherhand follow a dramatically different path. They must comply with the then existing norms of their fields. New ideas in academia, especially ones contradicting existing norms may be an anathema. Thus, we often see in Academia a lemming effect of large groups espousing common ideas. Rarely do we see the outlier.

In contrast an amateur is one who may have been educated and even an accepted expert in another field who use their skills in a field in which they receive no third-party compensation. Amateurs are now belittled because the Academy does not engage them. However, one need look no further than Darwin and Einstein, both amateurs when they did their seminal work. Darwin was not an academic, his work was independent. Einstein in 1905 was a Patent Clerk. Look at Watson and Crick, one a post-doc and the other a doctoral student. Neither yet fully accepted in the clan. Thus, not all amateurs are alike, but they should be judged on their merits not on their paychecks.

Now experts may themselves be limited. The more "expert" a person is the more likely they are expert quite deeply in their own paradigms, to use the Khunian term. They have a world view and everything must true up with that world view.

In contrast the well-educated amateur may have a much broader view, and an expertise readily applied to many areas. Take a venture capitalist. They look at a broad base of new technologies. They invest their own money, the proverbial skin in the game if you will, and thus must perform due diligence on the proposed investment. Thus, the must know the market, the technology, the people and the psychology of the people, the financial models and the like. VCs must have a broad and ever-changing set of intellectual assets to deal with an ever-changing technology base. Thus, one may ask; would not a VC be more useful that an academic in looking at a dramatically new pandemic such as COVID?

Now there are critics such as the one who opined below[17]:

Which is why we find myself increasingly obsessed with the rise of the so-called "COVID influencer" or armchair epidemiologist. These men — and they are, largely, men — are legitimate experts in other fields. They are lawyers, former reporters and thriller writers, Silicon Valley technologists, newspaper columnists, economists and doctors who specialize in different parts of medicine. Their utter belief in their own cognitive abilities gives them the false sense that their speculation, and predictive powers, are more informed than the rest of ours.

Normally, the consequences vary from annoying to infuriating, especially if you are a woman with expertise being mansplained by someone who knows less than you do. But when such displays of massive overconfidence and wrongheadedness reach the highest echelons of government, it can be downright dangerous. These behavioral displays were famously described in a December 1999 paper titled "Unskilled and unaware of it: how difficulties in recognizing

[17] https://www.insidehook.com/article/news-opinion/david-dunning-armchair-epidemiologists-coronavirus

one's own incompetence lead to inflated self-assessments" by two social psychologists at Cornell University, David Dunning and Justin Kruger. The effect they described was — and is — so pervasive that it's now named after them: the Dunning-Kruger effect.

Now what is this Dunning-Kruger Effect. According to Wikipedia, we chose this as the most available so bear with me, it is:

In the field of psychology, the Dunning–Kruger effect is a cognitive bias in which people with low ability at a task overestimate their ability. It is related to the cognitive bias of illusory superiority and comes from the inability of people to recognize their lack of ability. Without the self-awareness of metacognition, people cannot objectively evaluate their competence or incompetence[18]. From their paper they note:

People tend to hold overly favorable views of their abilities in many social and intellectual domains. The authors suggest that this overestimation occurs, in part, because people who are unskilled in these domains suffer a dual burden: Not only do these people reach erroneous conclusions and make unfortunate choices, but their incompetence robs them of the metacognitive ability to realize it. Across 4 studies, the authors found that participants scoring in the bottom quartile on tests of humor, grammar, and logic grossly overestimated their test performance and ability. Although their test scores put them in the 12th percentile, they estimated themselves to be in the 62nd. Several analyses linked this miscalibration to deficits in metacognitive skill, or the capacity to distinguish accuracy from error. Paradoxically, improving the skills of the participants, and thus increasing their metacognitive competence, helped them recognize the limitations of their abilities.

It is worth parsing this a bit. First the Wiki definition is kind. It limits those to be critiqued. Whereas the psychologists view is panhuman. They state again:

People tend to hold overly favorable views of their abilities in many social and intellectual domains.

That is not limited to those of limited expertise in other domains but all people, except perhaps the so-called "experts". Thus, one could infer from this definition that say one trained in engineering and medicine should have no opinion of the law or finance unless they were trained. That begs another question; how far should they be trained? Do they need doctoral degrees, post-docs, faculty positions, Nobel Prizes. Perhaps these two experts themselves have fallen into the very trap they accuse the rest of humanity of?

In the above, it is clear that the first author presents their bona fides as one who first off has a problem with men. Then the author seems to indicate that since someone who is an expert in some other field cannot under any circumstances opine on epidemiology. After all the psychologists have spoken. They are Academic experts, whereas our VC as noted above is just

[18] Kruger and Dunning, Unskilled and unaware of it: How difficulties in recognizing one's own incompetence lead to inflated self-assessments., Journal of Personality and Social Psychology, 77(6), 1121–1134.

rich as a result of their broad-based expertise. VCs often have great insight into the obvious whereas Academic Experts have knowledge of the arcane.

Wrongheadedness is an interesting turn of phrase. we will not try to project the author's venom onto any specific person but it is clear that this pandemic is a complex and multifaceted stochastic process. Namely as we once said in the Preface of my first book, "The world is filled with uncertainty." and little did we know how true that would be. This pandemic is truly uncertain. It is uncertain to have it is transmitted. It most likely is complex. It is uncertain as to its pathology. It is uncertain as to its prevalence.

No models seem to meet the ability to predict anything. The models lack socioeconomic, psychometric, and other factors which are dominant. Say we really do not know is fine, but people regrettably demand answers and unfortunately there are a wrath of Academics to opine with answers. Just having MIT or Harvard on your paycheck does not guarantee that your answer is true, and in fact you and not falling under the aforementioned condition, you are just wrong and have too much hubris as an expert.

Let us return to Kruger-Dunning. They stated:

Not only do these people reach erroneous conclusions and make unfortunate choices, but their incompetence robs them of the metacognitive ability to realize it.

Simply stated, if you permit me, it says: they don’t know it and they don't know they don't know it, whatever it is.

we would agree that such an effect may occur. On need just sit in any bar in the Bronx and one gets lots of these folks. we observed this in my youth. Go and listen to a cable news program, any new program in fact, and one has a massive amount of these people. But that is not how science is done. Science is done in a true combative mode of conjecture and fact, of one set of these battling another and the barrier between expert and amateur is truly non-existent. Einstein was not totally rejected in 1905 because he was a Patent Clerk. His papers were not stylistically overburdened as were so many German academics. They were brilliantly simple and clear.

Thus, is there are place for these amateurs? we would argue more today than ever before. The current pandemic is filled with unknowns. Let everyone have a swing at them. A credible amateur or even an expert should more than agree with that. Lawyers, doctors, VCs and yes engineers and physicians may have insight into the obvious that the academic expert is blind to. Denigrating experts in other fields is not only a rather hostile approach it is in my opinion a self-denigrating statement of one's personal inferiority.

We need all hands-on-deck if you will. Both amateurs and experts.

7.8 USELESS MODELS

We have seen that the models used at the beginning of this pandemic have proven to be useless. Moreover, they created massive over and under responses. This pandemic is very complex. It

intertwines many demographic subclasses as well as psychographic elements. As we have demonstrated in the New Jersey data, the facts, noisy as they may be, no modelling has even approached meeting this model. Mortality rates were high then collapsed.

The result of the academic models and their grossly incompetent results is a loss of any public confidence. We have see massive egos prognosticate on the future, we are told to trust the science, and then we see that the facts are no where near what we were told. Frankly we are in unchartered waters and the best we can say is "We don't know".

The worst part of the entire efforts was to trust the scientists. As anyone who has worked with scientists know they always change their minds as new information is obtained. Science is not some dogmatic set of divine rules. It is a Hegelian process of thesis, antithesis, and synthesis, and then start all over again. Science is ever changing, especially if it is doing its job.

The problem with models is human behavior. Models make assumptions that all humans are alike but we know there are dramatic differences and it is these regional and cultural differences that cause havoc with many models. We believe that the best that can be done is to have open and transparent data which can be analyzed and discussed and compared between large groups. This is an opportunity not only for the professional (namely one paid to do the job) but also the amateur (one who is equally competent but whose living is not contingent upon the work performed). The more eyes on the data the more opportunities to see things and the more trust the citizens will have. Science is not God given religion with certain scientists being high priests. Science is and should be an ongoing intellectually challenging attempt to better understand nature.

We must admit that the models used early on were not only useless but caused improper policy decisions. In addition the models and their after effects reduced the public trust and respect for science, justifiably so in many cases.

7.9 SCHOOLS, VACCINES, AND THE VIRUS

In order to reopen schools one must consider infecting students and teachers. One must al recognize that there still is a great deal unknown regarding the transmission of this virus and that there exists a large

7.9.1 Facts

The following is a list of what we call "facts". In reality there is no real clinical evidence of these "facts" and for the most part they are putative and lacking in any accepted scientific basis. However, they represent a reasonable starting point.

1. The virus is believed to be spread from one person to another by means of aerosolized particle containing the virions. We think. Some say not on surfaces but there is NO real scientific data showing this. There are tons of one off examples of things.

2. Asymptomatic patients can aerosolize virions unknowingly. We now believe that asymptomatics are true carriers. How long can they be carriers we do not know. Is this a Typhoid Mary syndrome?

3. Masks are not necessarily protective for uninfected individuals. Virions can still enter the body possibly by attachment to hands and then to the nasal areas as well as possible entry via the eyes. Also virions may attach to clothing and las for periods of unknown length.

4. Masks may reduce the virion load aerosolized from infected individuals. However, many masks are quite limited in this capacity and there is no clinical proof of the effectiveness of masks on infected people. Most masks are limited in blocking incoming virions. They may reduce outgoing but there is NO well described scientific proof.

5. Both children and adults are subject to infection and may suffer serious sequellae.

6. Primary and Secondary teachers are often in close contact with students perforce of the nature of teaching in today's education environment. The proximity is frequent and subjects the uninfected to significant risk of infection.

7. Teachers are often in compromised physical condition. The prevalence of T2 diabetes, asthma, obesity, coronary issues, age, stress, and excess exposure places many teachers at an excess level of risk if subsequently infected.

8. Students in the current educational environment have been trained to be interactive and lack significant discipline. Thus, students present a highly uncontrolled risk factor unless significant mitigation methods are employed.

9. Parents share in the uncontrolled risk pool. Many parents have eschewed proper risk mitigation and students may be recklessly exposed to viral infections. This become an unknowable.

10. Thus the school environment represents a high-risk environment of totally uncontrolled risk mitigation factors beyond the control of the teachers who are individually placed at substantial personal jeopardy.

7.9.2 Proposal for Risk Mitigation

We now present a set of possible proposals for risk mitigation. Again we must not that despite the publicity of the need for science and numbers, both are lacking in the real world. There is not clear scientific understanding of the infection process nor is there any accepted metrics for infection mitigation. The following are suggestions based logically upon what we think we know and what may be useful. These are subject to change.

7.9.3 Protection of the teacher.

To protect the teacher the following should be observed:

1. The teacher should have face masks as well as eye protection.

2. Hand sanitizers should be used and these should be based upon 91% isopropyl alcohol and glycerine. Glove may be a useful alternative.

3. Teacher temperatures should be taken daily, once in the start of school and one at the end of the school day.

4. RTPCR or equivalent viral tests should be performed weekly. The results should be returned no later than 48 hours after the test is performed and the teacher and school must have access to the results.

5. Teachers with possible risk factors should receive monthly mitigation reviews with their physicians.

6. Teachers should have physical mitigation interfaces using such devices as desk isolation unites.

7. Teachers should remove school attire before leaving the school premise and possibly even shower with disinfectants in a secure facility carefully cleaned. Clothing may be a vector for the virions.

8. All school facilities must be cleansed every night prior to the next day classes. The same about student means of transportation. There must be school agents monitoring student behavior on any transportation to minimize spread.

7.9.4 Protection of the Student.

To protect the student the following should be observed.

1. Daily temperature tests should be performed and recorded at the beginning and end of the school day

2. Weekly RTPCR or equivalent viral tests should be performed and the results made available to the school, teacher, and parents/guardians.

3. Students with elevated temperatures and/or positive viral tests should be immediately sent home by initially isolating them and notifying their parents. In the event of an elevated temperature a viral test must be performed withing six hours.

4. Notice of an infected students must be sent to all parents withing twelve hours after receipt, time being of the essence.

5. Students must be limited in class movement. Isolation by means of barriers must be employed where possible.

6. All students must wear masks of a type adequate to minimize viral spread from an infected student.

8 REFERENCES

1. Abbas et al, Basic Immunology, Elsevier, 4th Ed, 2014
2. Ahammad and Lira, Designing a novel mRNA vaccine against SARS-CoV-2: An immunoinformatics approach, International Journal of Biological Macromolecules 162 (2020) 820–837
3. Alter et al, Whither COVID-19 Vaccines, Nature Biotechnology, VOL 38, OCTOBER 2020, 1132–1145
4. Amiri and Richmond, Role of nuclear factor-κB in melanoma, Cancer Metastasis Rev. 2005 June; 24(2): 301–313
5. Barbosa et al, Co-activation of NF-κB and MYC renders cancer cells addicted to IL6 for survival and phenotypic stability, April 13, 2020, https://www.biorxiv.org/content/10.1101/2020.04.12.038414v1
6. Brunton et al, Therapeutics, 13th Ed, McGraw Hill, 2018
7. Byron et al, Translating RNA sequencing into clinical diagnostics: opportunities and challenges, Nature Review Genetics, May 2016
8. CDC, CDC 2019-Novel Coronavirus (2019-nCoV) Real-Time RT-PCR Diagnostic Panel, Feb 2, 2020
9. Chen, Y., et al, TMPRSS2, a Serine Protease Expressed in the Prostate on the Apical Surface of Luminal Epithelial Cells and Released into Semen in Prostasomes, Is Misregulated in Prostate Cancer Cells, The American Journal of Pathology, Vol. 176, No. 6, June 2010
10. Chong et al, Transmissibility of coronavirus disease 2019 (COVID-19) in Chinese cities with 2 different transmission dynamics of imported cases, https://www.medrxiv.org/content/10.1101/2020.03.15.20036541v1
11. Chonov et al, IL-6 Activities in the Tumour Microenvironment, Part we, Jrl Med Sci, Jul 30, 2019; 7(14)
12. Clark and Pazdernik, Biotechnology, Academic, 2nd Ed, 2016
13. Collier et al, Human Virology, 4th Ed, Oxford, 2011
14. Corbett et al, SARS-CoV-2 mRNA Vaccine Development Enabled by Prototype Pathogen Preparedness, bioRxiv preprint doi: https://doi.org/10.1101/2020.06.11.145920; this version posted June 11, 2020, Nature 22 October 2020
15. Corman et al, Diagnostic detection of 2019-nCoV by real-time RT-PCR, https://virologie-ccm.charite.de/en/ , Berlin, Jan 17, 2020
16. Dalton et al, Pre-emptive low cost social distancing and enhanced hygiene implemented before local COVID-19 transmission could decrease the number and severity of cases, https://ssrn.com/abstract=3549276

17. Dong et al, Development of humanized tri-specific nanobodies with potent neutralization for SARS-CoV-2, Scientific Reports (Nature) 2020 (10:17806)
18. Dong et al, Epidemiological Characteristics of 2143 Pediatric Patients With 2019 Coronavirus Disease in China, Pediatrics. 2020
19. Emanuel et al, An ethical framework for global vaccine allocation, Science, 11 September 2020.
20. Flynn et al, Activation of Toll-like Receptor 2 (TLR2) induces Interleukin-6 trans-signaling, Scientific Reports, (2019) 9:7306
21. Garbers et al, Interleukin-6: Designing Specific Therapeutics For A Complex Cytokine, Nature Reviews Drug Discovery volume 17, pages395–412(2018)
22. Gorlach et al, Reactive oxygen species, nutrition, hypoxia and diseases: Problems solved? RedoxBiology6(2015)372–385
23. Grein et al, Compassionate Use of Remdesivir for Patients with Severe Covid-19, NEJM, April 10, 2020
24. Guan et al, Clinical Characteristics of Coronavirus Disease 2019 in China, NEJM, Feb 28, 2020
25. Heil et al, Species-Specific Recognition of Single-Stranded RNA via Toll-like Receptor 7 and 8, Science, March 5, 2004
26. Heinrich et al, Principles of interleukin (IL)-6-type cytokine signalling and its regulation, Biochem. J. (2003) 374, 1–20
27. Hoffman et al, SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor, Cell, April 16, 2020
28. Hofmann and Clokie, Principles and Techniques of Biochemistry and Molecular Biology, 8th Ed, Cambridge, 2018
29. Holbrook et al, Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1, NEJM, March 17, 2020Hotchkiss and Opal, Activating Immunity to Fight a Foe, NEJM, March 26, 2020
30. Iwata-Yoshikawa et al, TMPRSS2 Contributes to Virus Spread and Immunopatholgy in the Airways of Murine Models after Coronavirus Infection, Jrl Virology, March 2019
31. Karin and Staudt, NF-kB, CSHL Press, 2010
32. Kiecolt-Glaser et al, Chronic stress and age-related increases in the proinflammatory cytokine IL-6, PNAS, 2003, vol. 100, no. 15
33. Ko et al, Androgen-Induced TMPRSS2 Activates Matriptase and Promotes Extracellular Matrix Degradation, Prostate Cancer Cell Invasion, Tumor Growth, and Metastasis, Cancer Res; 75(14) July 15, 2015
34. Koma et al, How Many Adults Are at Risk of Serious Illness If Infected with Coronavirus?, KFF, March 2020
35. Korpelainen et al, RNA-seq Data Analysis, CRC Press, 2015

36. Kupferschmidt and Cohen, Race to find COVID-19 treatments accelerates, Science, March 30, 2020.

37. Le et al, DA Approval Summary: Tocilizumab for Treatment of Chimeric Antigen Receptor T Cell-Induced Severe or Life-Threatening Cytokine Release Syndrome, The Oncologist, 2018, 23, 943-947

38. Leonard and Schreiber, Cytokines, CSHL Press, 2018

39. Letko et al, Functional Assessment of Cell Entry and Receptor Usage for SARS-CoV-2 and Other Lineage B Betacoronaviruses, Nature Microbiology, Feb 24, 2020

40. Li et al, Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia, NEJM, Jan 29, 2020

41. Li et al, Propagation analysis and prediction of the COVID-19, https://www.medrxiv.org/content/10.1101/2020.03.14.20036202v1

42. Li, Structure, Function, and Evolution of Coronavirus Spike Proteins, Annu. Rev. Virol. 2016. 3:237–61

43. Liu, et al, Oncogenic BRAF regulates b-Trcp expression and NF-kB activity in human melanoma cells, Oncogene (2006), 1–5.

44. Lund et al, Recognition of single-stranded RNA viruses by Toll-like receptor 7, PNAS, April 13, 2004, vol. 101, o. 15

45. Maruggi et al, mRNA as a Transformative Technology for Vaccine Development to Control Infectious Diseases, Molecular Therapy Vol. 27 No 4 April 2019

46. Mascola and Fauci, Novel vaccine technologies for the 21st century, Nature Reviews, Immunology, Feb 2020

47. McGarty, A Primer for COVID-19, March 2020, https://www.telmarc.com/Documents/White%20Papers/173Corona.pdf

48. McGarty, IL-6, COVID-19, Cytokine Storms and Galen, April 2020, https://www.researchgate.net/publication/340607207_IL-6_COVID-19_Cytokine_Storms_and_Galen

49. McGarty, Cancer Immunotherapy: A Systems Approach, https://www.researchgate.net/publication/314090163_Cancer_Immunotherapy_A_Systems_Approach

50. McGarty, CAR-T Cells and Cancer, October 2016, https://www.researchgate.net/publication/309419224_CAR_T_Cells_and_Cancer

51. Mehta et al, COVID-19: consider cytokine storm syndromes and immunosuppression, Lancet, March 28, 2020

52. Merle, N., Et Al, Complement System Part we: Role In Immunity, Frontiers In Immunology, June 2015, Volume 6, Article 262

53. Mizumoto et al, Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020, www.eurosurveillance.org

54. Morens and Fauci, Emerging Pandemic Diseases: How We Got to COVID-19, Cell, 3 September 2020

55. Murray. Mathematical Biology, Springer, 1989, pp 610-650.

56. Nishiura et al, Estimation of the asymptomatic ratio of novel coronavirus infections (COVID-19), International Journal of Infectious Diseases, Feb 13, 2020

57. Oxford et al, Human Virology, 5th Ed, Oxford, 2016

58. Pardi et al, mRNA vaccines — a new era in vaccinology, Nature Reviews, Drug Discovery, 12 January 2018

59. Perkins, Estimating unobserved SARS-CoV-2 infections in the United States, https://www.medrxiv.org/content/10.1101/2020.03.15.20036582v1

60. Pfefferle and Huntington, You Have Got a Fast CAR: Chimeric Antigen Receptor NK Cells in Cancer Therapy, Cancers 2020, 12, 706

61. Prager, Practical Pharmaceutical Engineering, Wiles, 2019

62. Puel and Casanova, The nature of human IL-6, J. Exp. Med. 2019 Vol. 216 No. 9 1969–1971

63. Rhodes, Type 2 Diabetes—a Matter of b-Cell Life and Death?, Science, 21 Jan 2005

64. Rincon, Special issue on Interleukin-6 (IL-6), International Journal of Biological Sciences, 2012; 8(9):1225-1226

65. Rothe et al, Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany, NEJM, Jan 20, 2020

66. Schlake et al, Developing mRNA vaccine technologies, RNA Biology, Nov 2012

67. Schoeman and Fielding, Coronavirus envelope protein: current knowledge, Virology Journal, (2019) 16:69

68. Shin et al, COVID-19 vaccine development and a potential nanomaterial path forward, Nature Nanotechnology | Vol 15 | August 2020 | 646–655

69. Shin et al, COVID-19 vaccine development and a potential nanomaterial path forward, Nature Nanotechnology, August 2020

70. Shmerling, An 81-Year-Old Woman With Temporal Arteritis, JAMA, June 7, 2006—Vol 295, No. 21

71. Smollen et al, Targeting IL-6: A review of data, Considerations Med 2018;2:12–18

72. Sompayrac, How the Immune System Works, 5th Ed, Wiley, 2016

73. Studebaker et al, Fibroblasts Isolated from Common Sites of Breast Cancer Metastasis Enhance Cancer Cell Growth Rates and Invasiveness in an Interleukin-6–Dependent Manner, Cancer Res 2008; 68: (21). November 1, 2008

74. Su et al, nterleukin-6 Signaling Pathway and its Role in Kidney Disease: An Update, Front. Immunol. 8:405, April 2017

75. Sullenger and Nair, From the RNA world to the clinic, Science, 17 June 2016

76. Sun et al, Understanding of COVID-19 based on current evidence, J Med Virol. 2020;1–4.

77. Sungnak et al, SARS-CoV-2 Entry Genes Are Most Highly Expressed in Nasal Goblet and Ciliated Cells within Human Airways, Wellcome Sanger Inst, Cambridge, UK, Feb 2020

78. Tak and Firestein, NF-kB: a key role in inflammatory diseases, J Clin Invest. 2001;107(1):7-11

79. Takeda and Akira, Toll-like receptors in innate immunity, International Immunology, Vol. 17, No. 1, pp. 1–14, 2005

80. Tan et al, Respiratory Viral Infections in Exacerbation of Chronic Airway Inflammatory Diseases: Novel Mechanisms and Insights from the Upper Airway Epithelium, Front in Cell and Dev Bio, Feb 2020

81. Tanaka and Kishimoto, Targeting Interleukin-6: All the Way to Treat Autoimmune and Inflammatory Diseases, International Journal of Biological Sciences, 2012; 8(9):1227-1236

82. Tisoncik et al, In the Eye of the Cytokine Storm, MMBR, Microbiology and Molecular Biology Reviews, March 2012

83. Tregoning et al, Vaccines for COVID-19, Clinical and Experimental Immunology, 202: 162–192, 2020

84. Vaduganathan et al, Renin–Angiotensin–Aldosterone System Inhibitors in Patients with Covid-19, NEJM, March 30, 220

85. Vaninov, In the Eye of the COVID-19 cytokine storm, Nature Reviews, Immunology, 6 April, 2020

86. Velazquez-Salinas et al, The Role of Interleukin 6 During Viral Infections, Frontiers in Microbiology, May 2019, Volume 10, Article 1057

87. von Essen et al, IL-6, IL-12, and IL-23 STAT-Pathway Genetic Risk and Responsiveness of Lymphocytes in Patients with Multiple Sclerosis, Cells 2019, 8, 285

88. Wang et al, Discovery of a subgenotype of human coronavirus NL63 associated with severe lower respiratory tract infection in China, 2018, in Emerging Microbes & Infections, Taylor and Francis, Jan 2020

89. Wang et al, International expansion of a novel SARS-CoV-2 mutant, medRxiv preprint doi: https://doi.org/10.1101/2020.03.15.20035204 .

90. Wolfel et al, Virological assessment of hospitalized cases of coronavirus disease 2019, medRxiv preprint doi: https://doi.org/10.1101/2020.03.05.20030502

91. Wu et al, A new coronavirus associated with human respiratory disease in China, Nature, Feb 3, 2020

92. Wu et al, Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China, JAMA Internal Medicine, March 13, 2020

93. Xing et al, IL-6 is an antiinflammatory cytokine required for controlling local or systemic acute inflammatory responses, J Clin Invest. 1998;101(2):311-320

94. Yan et al, Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2, Science, 27 March 2020

95. Zeng, et al, Bat Severe Acute Respiratory Syndrome-Like Coronavirus WIV1 Encodes an Extra Accessory Protein, ORFX, Involved in Modulation of the Host Immune Response, Journal of Virology, July 2016

96. Zhang et al, A Thermostable mRNA Vaccine against COVID-19' Cell 182, 1271–1283, 2020

97. Zhang et al, A Thermostable mRNA Vaccine against COVID-19, Cell, 3 Sept 2020

98. Zhou et al, A pneumonia outbreak associated with a new coronavirus of probable bat origin, Nature, 12 March 2020

99. Zhou et al, Back to the spring of Wuhan: facts and hope of COVID-19 outbreak, Frontiers Medicine, 21 Feb 2020

100. Zhu et al, A Novel Coronavirus from Patients with Pneumonia in China, 2019, NEJM Jan 24, 2020

9 INDEX

aAPC, 50
Ab, 36, 40, 58, 61
ACE2, 31
adaptive immune system, 36, 39
aerosol, 30, 60
Aerosols, 60
Ag, 36, 38, 39, 45, 58
antibody, 36, 42, 43, 44, 50, 56, 61
antigen, 36, 37, 44, 51, 52, 53, 57
APC, 36, 37, 38, 40
B cell, 37, 40, 57
bioreactors, 56
Black Plague, 9
CD4, 42
CD8, 42
CDC, 7, 29, 58, 59, 60, 62, 63, 64
China, 7, 74, 75, 77, 78
clinical trials, 51
Contact Tracing, 11
contamination, 56
Conventional mRNA Vaccines, 52
Corona, 6, 7, 30, 31, 32, 36, 49
COVID-19, 61, 63, 64, 76, 78
C-terminal, 36
cytokine storm, 42, 75, 77
cytokines, 42
Death Panels, 64
deaths, 6, 9, 17, 19, 23
density, 15
Descartes, 60
develop, 50, 53, 58, 62
Distribution, 60
DNA, 30, 45, 49, 52
DNA vaccines, 50
doubling time, 20, 21
Dover, 16
eggs, 44, 45
encapsulation, 53, 55, 56
epithelial, 31
esterase, 30
Fab, 37
Fair Priority Model, 64, 65
Fc, 37, 43, 58
Fc receptor, 43
FDA/EMA, 54
filtration, 53, 54, 56
Florham Park, 16
flu, 6, 9, 60
follicular, 42
glycoprotein, 30
Government, 7, 8, 9, 29, 62, 63, 65
haemagglutinin, 30
heavy chains, 36
herd immunity, 61
Hispanic, 15, 16
IgA, 42, 43, 61
IgG, 36, 42, 43, 61
immunoglobulin, 36, 61
Inactivated vaccines, 50
incidence, 9, 13, 23
infected, 7, 9, 14, 18, 21, 23, 30, 33, 58, 59, 60, 61, 70, 71, 72
light chains, 36
lipid polysaccharide, 45, 51
Live Attenuated, 50
LTC, 17, 19, 23, 60
MERS, 33, 42
MHC II, 38
monoclonal, 43, 53, 58
Morris County, 10
mRNA, 8, 33, 45, 49, 51, 52, 73, 78
mRNA vaccines, 8, 44, 49, 50, 51, 52, 54, 76
nanobodies, 58, 74
NEJM, 58, 59, 62, 74, 75, 76, 77, 78
New Jersey, 9, 60
normalized, 22, 23
N-terminal, 36
Obamacare, 64
ORFs, 42
pandemic, 30
Parsippany, 16
pathogen, 56
patients, 5, 23, 42, 43, 50, 53, 56, 58, 61, 70
PCR, 55, 73

Peptide, 50
phage, 58
Phasing, 60
Points of Delivery, 60
PoP, 26, 27
population, 6, 9, 14, 15, 16, 21, 58, 59, 63
prevalence, 9, 14, 17
produce, 29, 32, 33, 53, 57, 61
protein, 30, 32, 33, 34, 36, 45, 46, 47, 49, 51, 58, 76
Protein vaccines, 50
pseudovirus, 53, 58
receptors, 31, 33, 77
re-immunization, 61
rhinoviruses, 32
RNA, 30, 31, 32
safety, 42, 56
saRNA vaccines, 50
SARS-CoV-2, 58, 74
Scheduling, 60
school, 11, 23, 70, 71
science, 59, 62, 63, 70
Science, 59, 62, 74, 75, 76, 78
Self-Amplifying mRNA Vaccines, 52
single strand, 30, 31
single stranded, 30, 34
spike protein, 36, 43, 51, 53
T cell, 38, 39, 42, 50
T cell receptor, 38
T helper, 42
T helper cell, 40
target, 5, 23, 53, 64
T-cell, 59
TCR, 38
temperature, 32, 33, 50, 71
Testing, 5, 27, 28, 60
titration, 54
Tracking, 60
transmission, 6, 59, 69, 73
transparent, 29
vaccine, 5, 8, 44, 58, 59, 60, 62, 63, 64, 73, 74, 76
variolation, 59
viral vector, 47, 49
Viral vectored, 50
virion, 33, 34, 70
WHO, 29