COVID-19 and some basics of mathematical epidemiology

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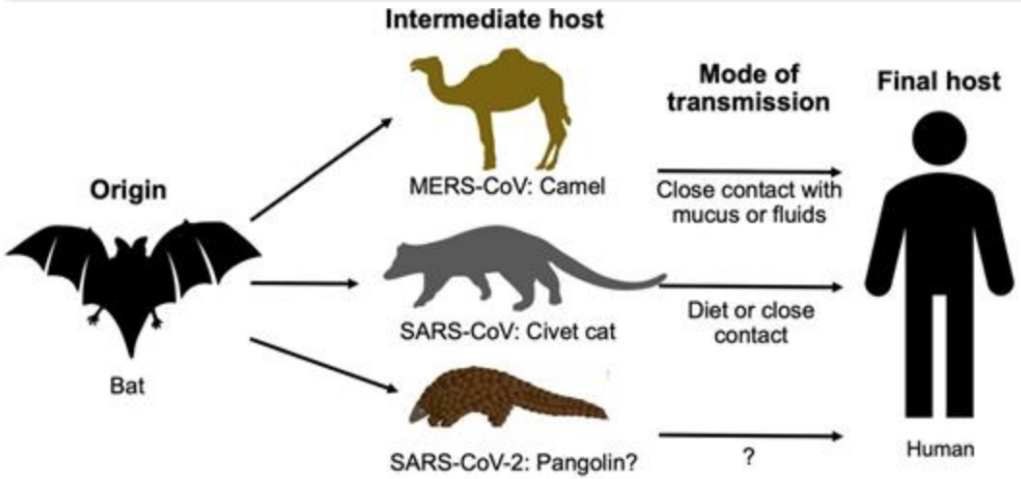
Burden of Some Infectious Diseases

Disease	Mortalities (Global)
Smallpox (430BC-1979)	$>$ 300 million in 19th century
Black Plague (1340-1771)	$>$ 75 million
Malaria (1600-Present)	$\approx$ 1-2 million annually
(Spanish) Flu Pandemic (1918-1919)	$>$ 50 million
COVID-19 (2019-Present)	$>$ 2 million

Coronavirus Pandemics

Coronaviruses occur naturally in mammal and birds; some coronaviruses cross species and become novel human viruses

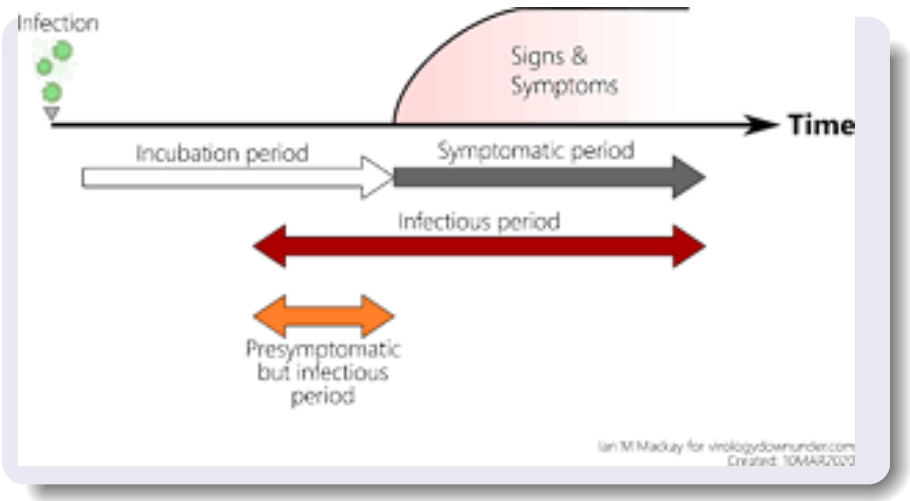


— Yi et. al., *Int J Biol Sci* 2020

COVID-19 spreads via respiratory droplets in the air -i.e., **airborne route**

Coronavirus Pandemics

	SARS-CoV	MERS-CoV	COVID-19 (SARS-CoV2)	Sources:
Duration	2002 - 2003	2012 - present	2019 - present	Gumel et al, 2020
Incubation Period (infected to symptoms (if any))	2-7 days	5 days	**2-14 days**	Kakodkar, Kaka & Baig,2020
Deaths	744 (global)	866 (global)	**486,321 (USA)** **2,407,869 (global)**	
Confirmed Cases	8000 (global)	2519 (global)	**27,692,967 (USA)** **109,155,627 (global)**	Johns Hopkins University
Countries	29	27	All (220)	



Asymptomatic and Pre-symptomatic can **spread and NOT show symptoms**

Why Mathematical Modeling?

Mathematical models help to understand and analyze the spread and behavior of diseases

Not enough to just collect and analyze data; must combine and build a model to try to capture and understand how the disease evolves

Public Health Practitioners Set the Foundation

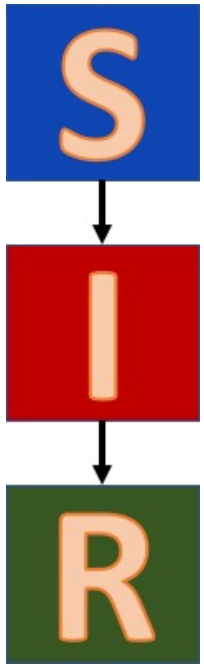
- Daniel Bernoulli (1760) developed a model of smallpox transmission and control
- John Snow (1855) argued that cholera was not an airborne disease and via mapping, he found a town's outbreak to be the source of a water pump
- Ross's model (1916) explains the relationship between the number of mosquitoes and incidence of malaria in humans
- Pyotr Dimitrievich En'ko (1889) developed a model of the measles epidemics
- Sir Ronald Ross (1908) published a dynamic malaria model Olgilvy Kermack(Scottish biochemist) and Anderson Grey McKendrick(Scottish military physician and epidemiologist) published work on their mathematical epidemiological model in 1927

Kermack-McKendrick (KM) SIR Model

$$\frac{dS}{dt} = -\beta SI$$

$$\frac{dI}{dt} = \beta SI - \gamma I$$

$$\frac{dR}{dt} = \gamma I$$



Total population is divided into mutually-exclusive sub-populations (called compartments):

- S denotes the susceptibles (can be infected)
- I denotes the infectives (infected and infectious (can spread))
- R denotes the recovered (removed (immune))
- $\beta > 0$, effective contact rate; $\gamma > 0$, recovery rate

Kermack-McKendrick (KM) SIR Model:Main Assumptions

- each individual has equal chance of interacting with any other (homogenous mixing)
- large population size (else stochastic effects dominate)
- exponentially-distributed waiting times in epidemiological compartments, for example, the infective period is exponentially distributed with mean

$$\int_0^\infty e^{-\gamma s} ds = 1/\gamma$$

  where γ leave the infective class and the fraction of infectives remaining infective s time units after having become infected is $e^{-\gamma s}$
- no entry into or departure from the population, except possibly by disease-induced deaths (closed population)
- time scale of the disease is assumed faster than the time scale of births and deaths (so that the impact of demographic effects on the population may be ignored)

Kermack-McKendrick (KM) SIR Model

$$\frac{dS}{dt} = -\beta SI$$

$$\frac{dI}{dt} = \beta SI - \gamma I$$

$$\frac{dR}{dt} = \gamma I$$

β = average number of contacts an infective makes per unit of time
$1/\gamma$ = average duration of infectiousness

KM Model explains the rapid rise and fall in the number of infected; shows that epidemics come and go and not every member of the population is affected

Kermack-McKendrick (KM) SIR Model

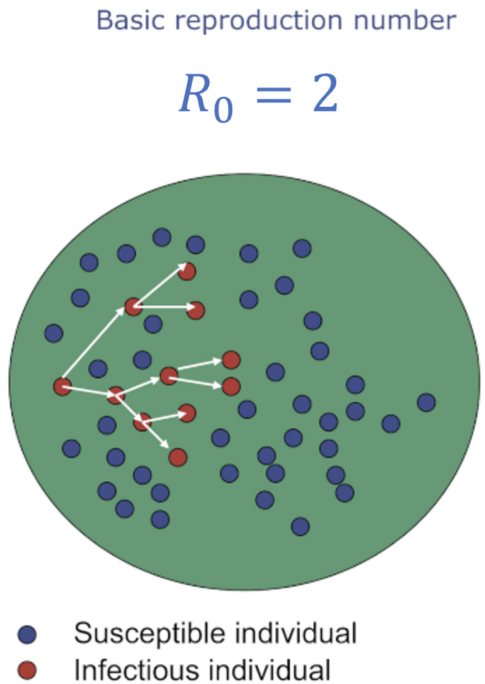
Since β = average number of contacts an infective makes per unit of time if $S(0) = N$, then, one infected individual will infect $\beta S(0) = \beta N$ individuals per unit time

Since the average duration of infectiousness = $1/\gamma$, an infected individual will remain infectious for an average time period of $1/\gamma$; thus, the average number of individuals a typical infective will in turn infect is $\frac{\beta S(0)}{\gamma}$.

That is, the (basic) reproduction number $R_0 = \frac{\beta S(0)}{\gamma}$

The basic reproduction number R_0

R_0 is the average number of secondary infections produced when one infected individual is introduced into a host population of susceptibles.



Epidemiological implication: disease can be effectively controlled if $R_0 < 1$ and disease persists if $R_0 > 1$

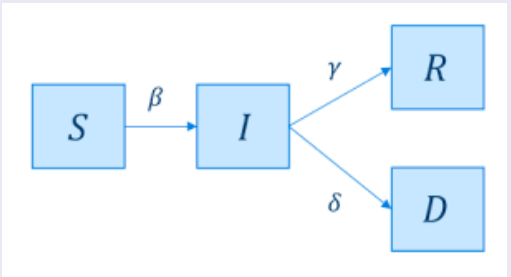
SIRD Model (as in code)

$$\frac{dS}{dt} = -\beta(S/N)I$$

$$\frac{dI}{dt} = \beta(S/N)I - \gamma I - \delta I$$

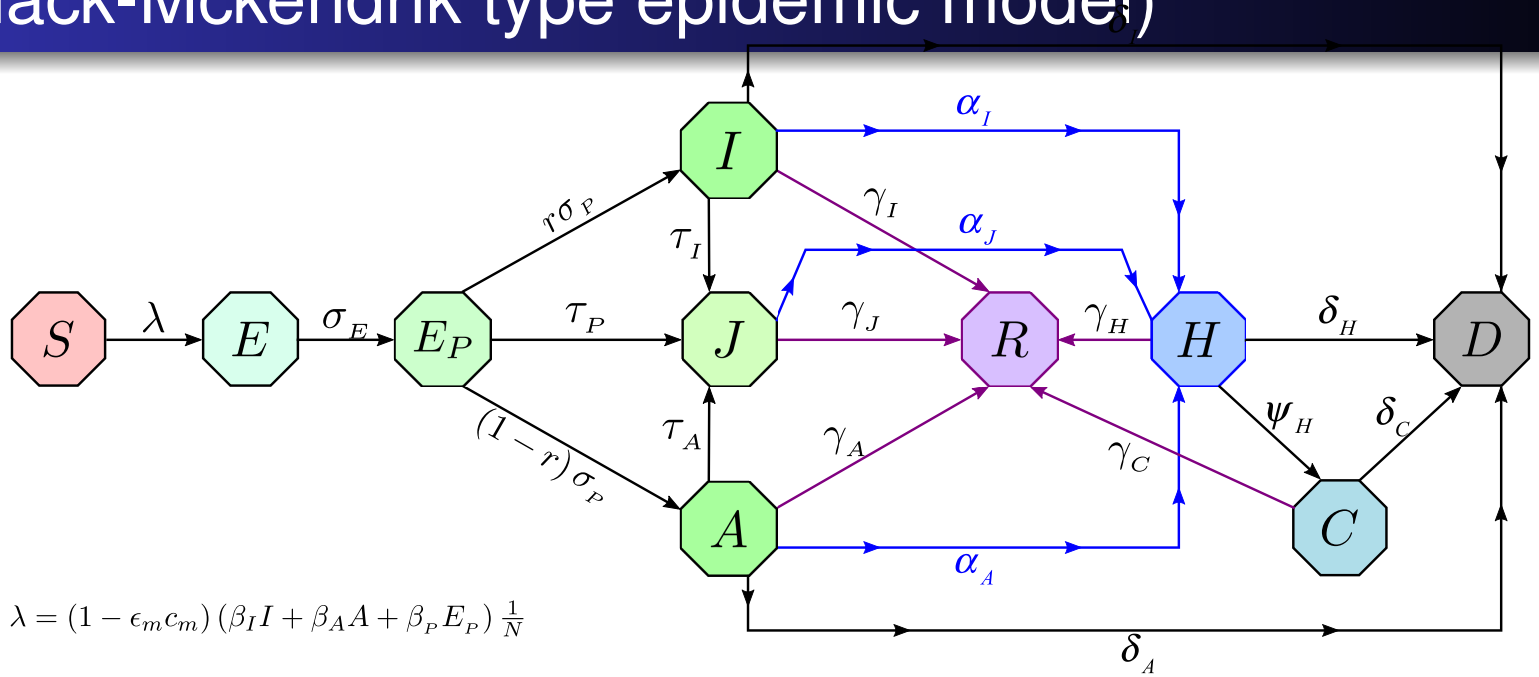
$$\frac{dR}{dt} = \gamma I$$

$$\frac{dD}{dt} = \delta I$$



- S denotes the susceptibles
- I denotes the infective (infected and infectious)
- R denotes the recovered
- D denotes deaths
- (β, γ, δ) are non-negative contact, recovery and death rates
- $N(t) = S(t) + I(t) + R(t)$

Flow Diagram for Model in paper (modified Kermack-Mckendrik type epidemic model)



State Variable	Description
S	Population of susceptible individuals
E	Population of exposed individuals (newly-infected but not infectious)
E_P	Population of presymptomatic (infectious) individuals
I	Population of symptomatically-infectious individuals
A	Population of asymptomatically-infectious individuals
J	Population of self-isolated infectious individuals
H	Population of hospitalized individuals
R	Population of recovered individuals
C	Population of individuals in intensive care unit (ICU)
D	Population of deceased COVID-19 individual

Model Formulation: Differential Equations

$$\frac{dS}{dt} = -\beta_I(1-\epsilon_m c_m)\frac{SI}{N} - \beta_A(1-\epsilon_m c_m)\frac{SA}{N} - \beta_P(1-\epsilon_m c_m)\frac{SE_P}{N} = -\lambda S$$

$$\frac{dE}{dt} = \beta_I(1-\epsilon_m c_m)\frac{SI}{N} + \beta_A(1-\epsilon_m c_m)\frac{SA}{N} + \beta_P(1-\epsilon_m c_m)\frac{SE_P}{N} - \sigma_e E = \lambda S - \sigma_e E$$

$$\frac{dE_P}{dt} = \sigma_e E - \sigma_p E_P - \tau_p E_P$$

$$\frac{dI}{dt} = r\sigma_p E_P - \alpha_I I - \tau_I I - \gamma_I I - \delta_I I$$

$$\frac{dA}{dt} = (1-r)\,\sigma_p E_P - \alpha_A A - \tau_A A - \gamma_A A - \delta_A A$$

$$\frac{dH}{dt} = \alpha_I I + \alpha_A A + \alpha_J J - \psi_H H - \gamma_H H - \delta_H H$$

$$\frac{dC}{dt} = \psi_H H - \gamma_C C - \delta_C C$$

$$\frac{dJ}{dt} = \tau_p E_P + \tau_A A + \tau_I I - \alpha_J J - \gamma_J J$$

$$\frac{dR}{dt} = \gamma_I I + \gamma_A A + \gamma_C C + \gamma_J J + \gamma_H H$$

$$\frac{dD}{dt} = \delta_A A + \delta_I I + \delta_H H + \delta_C C$$

Model Fitting & Parameter Estimation

Parameter	Description	Range	Baseline value
β_I	**Effective contact rate for symptomatically-infectious individuals**	FITTED	FITTED
β_A	**Effective contact rate for asymptomatically-infectious individuals**	FITTED	FITTED
β_P	**Effective contact rate for presymptomatically-infections individuals**	FITTED	FITTED
τ_A	**Rate at which asymptomatically-infectious humans self-isolate**	FITTED	FITTED
τ_P	**Rate at which presymptomatic infectious individuals self-isolate**	FITTED	FITTED
α_J	**Hospitalization rate for self-isolated individuals**	FITTED	FITTED

Table: **Parameters that are fitted using nonlinear least squares method.**

Other 18 parameters are estimated using literature and COVID-19 information.

Model Fitting & Parameter Estimation

We fit the model to the cumulative mortality data.

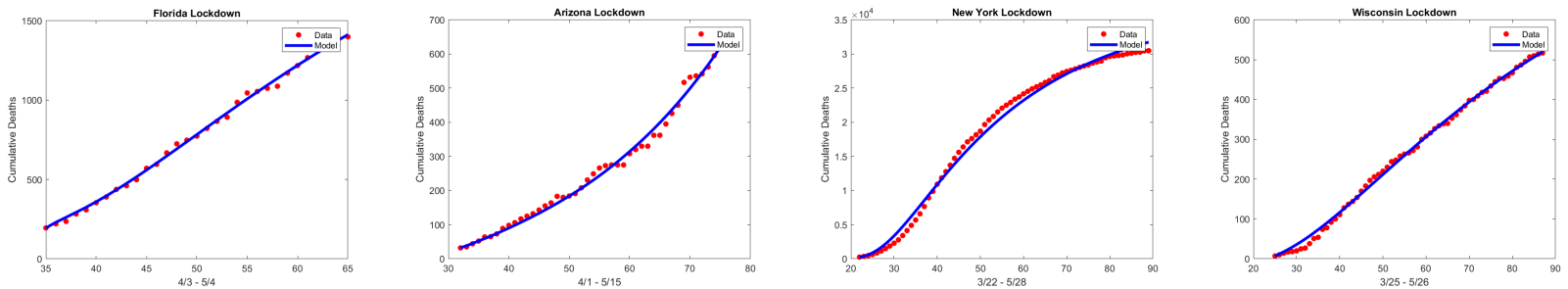


Figure: The lockdown period. The plots show the model (blue) against the data (red) over the respective lockdown periods.

Many Variations and Complexities

There are many variations and complexities to consider or include, e.g.,:

- No Immunity -e.g., SIS
- births and deaths (demographic effects)
- non-homogeneity - e.g, different effective contact rates β
- immunity - passive (from mother to child), partially/temporarily acquired,...
- partial differential equations - e.g. age dependent population growth so depends on age and time
- non deterministic features -i.e., add stochastic features

For example, in our paper, we focus on 3 infectious classes.

Main Drivers of spread in terms of daily cases? (in paper)

Pre-symptomatic & Asymptomatic population versus Symptomatic population.

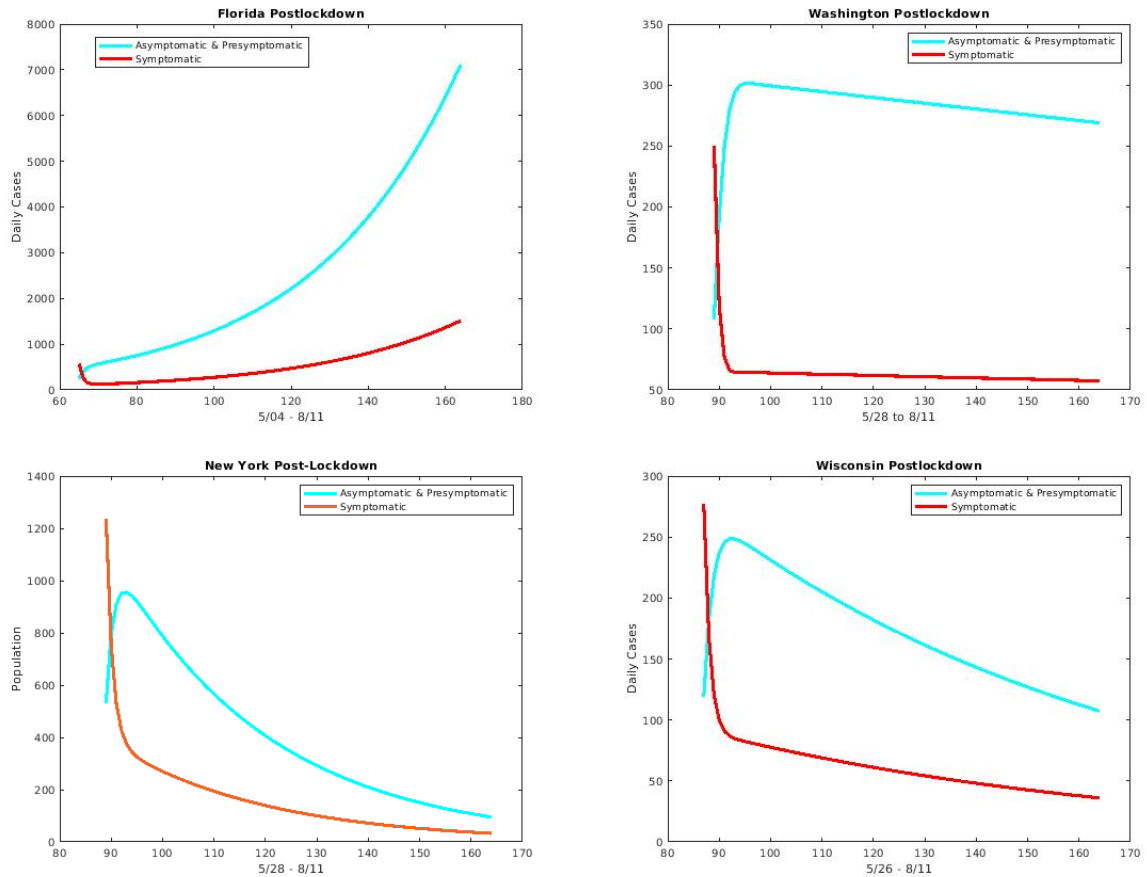


Figure: Daily cases. Pre-symptomatic & asymptomatic (cyan) versus symptomatic (red) for each state during their respective postlockdown period.

Main Drivers in terms of cumulative deaths or cases? (in paper)

We focus on the two groups separately.

- For pre-symptomatic/asymptomatic (green), let $\beta_I = 0$
- For symptomatic (magenta), let $\beta_A = 0$ and $\beta_P = 0$

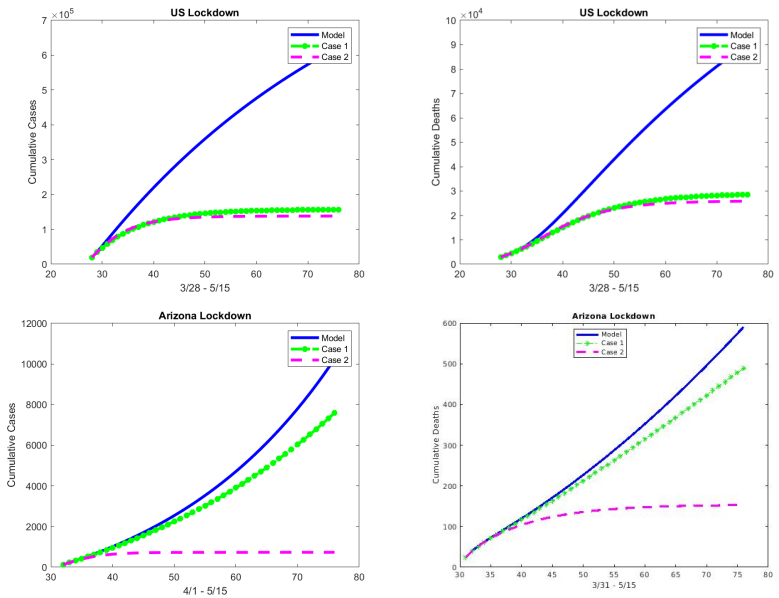


Figure: Cumulative cases and deaths for Arizona and the U.S. over the respective lockdown period.

Implications (in paper)

What happens when testing is increased?

- Increase testing of asymptomatic and presymptomatic individuals (green)
- Increase testing of symptomatic (magenta)

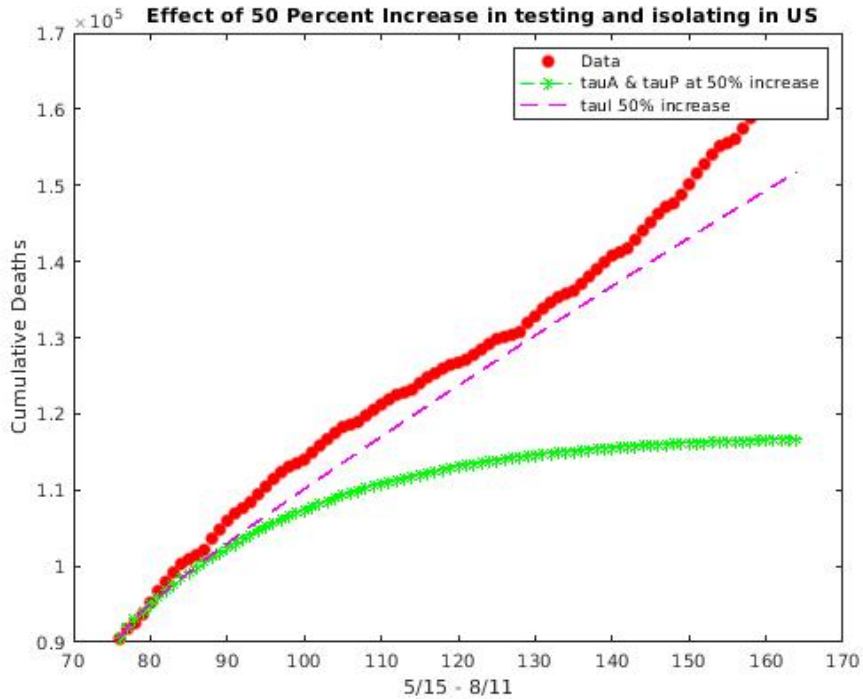


Figure: The effect of a 50 percent increase in testing of asymptomatic and presymptomic vs sympomtomatic individuals on the cumulative deaths in the US during post-lockdown.

Recap

Mathematical modeling of diseases to understand and analyze the spread, control and mitigation. Involves

- formulate model
- determine DEs and parameter values
- mathematical analysis and computations- qualitative dynamics (equilibria, asymptotic stability), calculation of R_0, etc.
- fit to data - parameter estimation
- numerical solutions, simulations, sensitivity and uncertainty analysis

R_0 for Some Infectious Diseases (WHO 2016)

R_0 (the basic reproduction number) - how many people, on average, an infectious person will in turn infect

Disease	R_0
COVID-19	2 -7? (nih.gov)
SARS	2-3
Ebola (2014)	1.5-2.5
HIV/AIDS	2-5
Measles	12-18
Mumps	4-7
Pertussis	12-17
Diptheria	6-7
Smallpox	5-7

How to stop the spread of COVID-19??

Containment & Mitigation strategies such as

- lockdown
- testing - widespread and frequent, isolation/quarantine
- face masks
- social distancing, limit mass gatherings, proper ventilation in enclosed space
- contact tracing - DIFFICULT unless number of infectious are small

Challenges:

- level of compliance
- spread without symptoms
- super-spreaders

Vaccines Cautions & Challenges

Vaccines!!
But how many and how fast to stop spread?

Want a large enough fraction (immunity fraction) to have immunity so that the virus can't spread (or mutate) significantly and thus the rest of (unvaccinated) population is protected -i.e., herd immunity is achieved.

$$\text{immunity fraction} = 1 - \frac{1}{R_0}$$

In general, as reproduction number (spread of virus) increases, then immunity fraction (required number to vaccinate) increases

If $R_0 = 2$ (the minimum), then immunity fraction $= \frac{1}{2}$, since U.S. population is about 331 million, need more than 150 million vaccinated - at 14 million on 2/15/2021.

Vaccines Cautions & Challenges

Some challenges and questions:

- vaccine distribution
- vaccine efficacy
- duration of vaccine immunity
- vaccine and infectiousness
- vaccine and different strains
- vaccine distribution & administration disparities - both national and global

Vaccines Cautions & Challenges - understanding fears

The Tuskegee Syphilis Experiment

- Conducted 1932-1972 in Tuskegee, AL by the US Public Health Service
- Recruited about 400 black men with syphilis to research natural progression of the untreated disease
  - Never told if they had syphilis nor were they treated for it
- Story broke out in the Washington Star on July 25, 1972
- In 1974 Congress passed the National Research Act to oversee and regulate human experimentation in medicine
- In 1997 HBO produces Miss Evers' Boys
- In May of 1997, President Clinton formally apologized

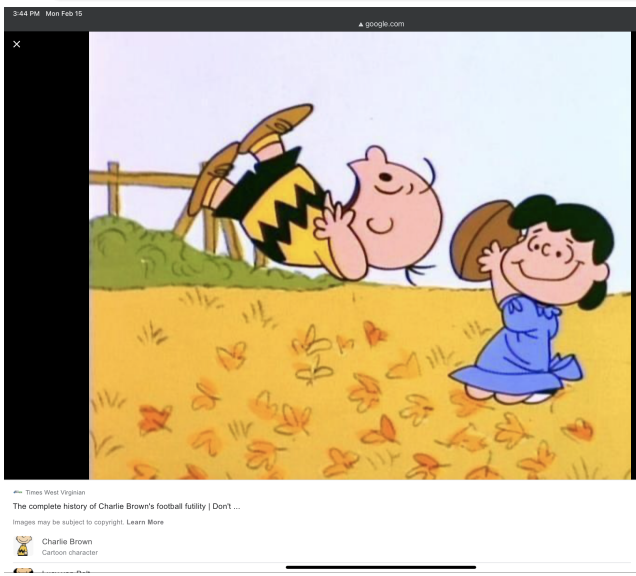
Some Vaccine Success Stories

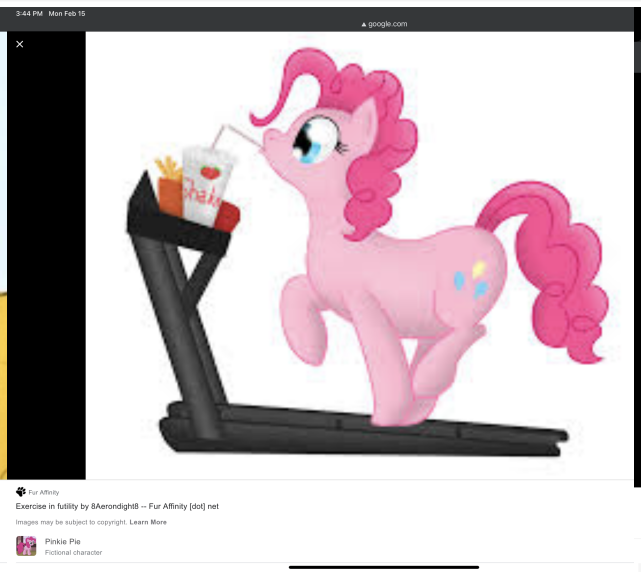
Disease	R_0	Herd Immunity Threshold & Vaccine Info
COVID-19	2 -7	50% - 86%
Measles	12-18	92% - 95% **"eliminated" (US 2000);20+yrs MMR**
Diptheria	6-7	83% - 86% **"nearly unheard of in US";DTAP, Tdap, Td**
Pertussis	12-17	92% - 94% **"outbreaks & peaks";DTaP, Tdap, Td**
Smallpox	5-7	80% - 86% **"eradicated" Worldwide 1980; (US 1952)**

- Diptheria vaccine prgm took 80+ yrs to eliminate it in US ; since 1920s
- Smallpox eradication took about 200 years
- Measles: about 400 - 500 deaths per year in US (recent outbreaks?); COVID-19: $>$ 450,00 deaths so far in US;

COVID-19 Vaccine Success!?

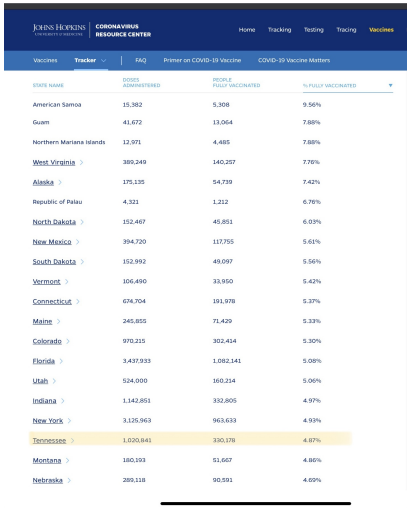
Vaccine-acquired herd immunity requires stopping the spread of virus, else it's like an exercise in futility.





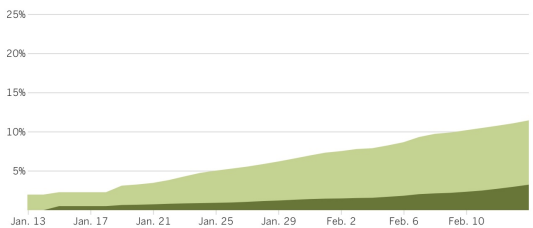
COVID-19 Vaccine Success!?

Fully vaccinated percentages are increasing but still considerably too low

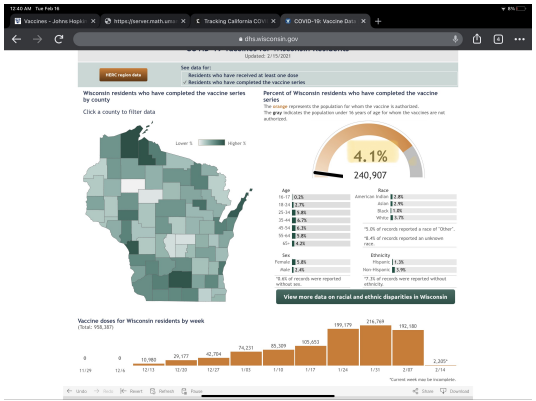


Of the roughly 40 million people who live in California, 4,493,220 have received at least one dose, or 11.4% of the total. Of those, 1,287,390, or 3.3%, have received the recommended second dose.

Percentage of Californians who have received one or two doses



Centers for Disease Control and Prevention



COUNTRY NAME	DOSES ADMINISTERED	PEOPLE FULLY VACCINATED	% FULLY VACCINATED
Israel	6,442,239	2,534,985	28.53%
Gibraltar	25,287	9,522	28.24%
Seychelles	51,819	13,867	14.33%
Cayman Islands	15,543	6,371	9.92%
United States	52,884,356	14,077,440	4.30%
Isle of Man	13,733	3,328	3.95%
Malta	50,175	15,601	3.22%
Denmark	398,024	167,506	2.88%
United Arab Emirates	5,055,231	250,000	2.59%
Bermuda	10,000	1,600	2.50%
Serbia	950,871	167,710	2.40%
Slovenia	118,399	47,647	2.30%
Romania	1,113,975	427,341	2.19%

Why Mathematical Epidemiology?

To understand and analyze emerging and re-emerging infectious diseases such as

- malaria
- ebola
- measles
- more coronaviruses??? due to
  - environmental degradation?
  - invasion of ecosystems?
  - climate change (global warming)?
  - increased global connections and interactions?

...we are constantly a short flight away from a serious epidemic. — Canadian Advisory Committee on SARS, 2003

THANK YOU!

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