

# CorVexit: What Way Forward?

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# Talk Outline

- Numbers in perspective
- Corona virus infections
- Six numbers we need to know
- Public health and contact tracing in the US. vs. South Korea
- The Corona virus and the clinical laboratory
  - Molecular and antibody testing
  - Predictive value of mass screening
  - Scaling test to run at a national level
- Social distancing, antivirals, vaccines and herd immunity
- Median age by country and why it matters
- CorVexit strategies and tradeoffs

# Two Quotes

- “Quantity has a quality all its own.”
- “Amateurs discuss strategy, professionals discuss logistics.”

# Numbers in Perspective

- Assuming 1 million infections
  - in a world of 7.3 billion people, then 0.014% of the population is infected
  - in a nation of 327 million people, then 0.31% of the population is infected
- U.S. deaths
  - Each year in the U.S. about 2.8 million people die
  - About 2 million Medicare beneficiaries die each year (generally over 65)
  - Each year:
    - About 20,000 to 60,000 deaths are flu related
    - About 67,000 are opioid fatalities
    - About 43,000 deaths are suicides
    - About 37,000 deaths are motor vehicle fatalities

# Numbers in Perspective

- Assuming a factory makes 10 million facemasks per week:
  - It takes 100 weeks to make 1 billion facemasks
  - In a nation of 327 million people, that is 3.06 masks per person

# Corona Virus Infections

See: [https://www.youtube.com/watch?v=8\\_bOhZd6ieM&t=26s](https://www.youtube.com/watch?v=8_bOhZd6ieM&t=26s)

- Large diverse family of viruses
  - 4 strains account for 10% to 15% of common colds
- Bats are a reservoir for corona viruses
  - We know of 500+ bat corona viruses, but 5,000+ are estimated to exist
  - The viruses can jump to humans, typically through an intermediate host
  - There have been 3 such jumps in the last 20 years
- Future jumps are very likely

# Corona Virus Infections

See: [https://www.youtube.com/watch?v=8\\_bOhZd6ieM&t=26s](https://www.youtube.com/watch?v=8_bOhZd6ieM&t=26s)

Name	Date	Intermediate Host	Worldwide Number of Cases	Deaths	Death Rate
SARS/Cov-1	Late 2002	Civet Cats	8098	774	9.6%
MERS/MERS-Corona Virus	2007	Dromedary Camels	2521	866	34%
CoV-2/Covid-19	2019/2020	?	?	?	Estimated between 0.7% and 4%

# Why Covid-19 is So Difficult

- Very infectious
  - Initial asymptomatic phase even if symptoms latter develop
  - Many infected individuals show no to minimal symptoms
- Lethal to a vulnerable subpopulation
  - Older, comorbid, male
  - Require intensive medical support to minimize the death rate
- No known treatment or vaccine
- Contrast to Ebola
- Corona virus research not a priority: <https://justthenews.com/politics-policy/coronavirus/while-nih-failed-test-coronavirus-drugs-it-studied-drunk-monkeys-soap>



# Public Health and Contact Tracing

- In the U.S. these are largely functions of state governments
- CDC offers support including laboratory testing for unique cases, guidance and best practices
- Do states have adequate personnel for contact tracing?
- Data sharing issues
  - Logistical and legal
- Contrast South Korea

# South Korea

From: <https://www.youtube.com/watch?v=gAk7aX5hksU&list=WL&index=108&t=0s>

- Experienced a MERS outbreak in 2015
- Bolstered laboratory capacity as a result
- Developed contact tracing methods
  - Used cell phone data
  - Used algorithms to interpret the data and probably run baselines?
  - Implemented focused laboratory testing
- Quarantine App!

# Six Numbers We Need to Know

1. What percent of the population has been exposed to the virus? **This is crucial for CorVexit as it is needed to answer the following two questions!**
2. Given 1 above, what percent of the general population is immune and cannot infect other people?
3. Given 1 above, what percent of the infected population will require hospitalizations?
4. What percent of hospitalized patients will require a ventilator?
5. What percent of hospitalized patients will die and how is this number dependent on the adequacy of the health care system?
6. How seasonal is the disease?

# Six Numbers We Need to Know

- Answers will vary across the U.S. given its varying demographics
- Random sampling with antibody testing at county level would be best but difficult to attain
- What sampling can we do?
- How might it vary by state?
- How do you test vulnerable populations (e.g. homeless)?

# Types of Test to Detect Corona Viruses

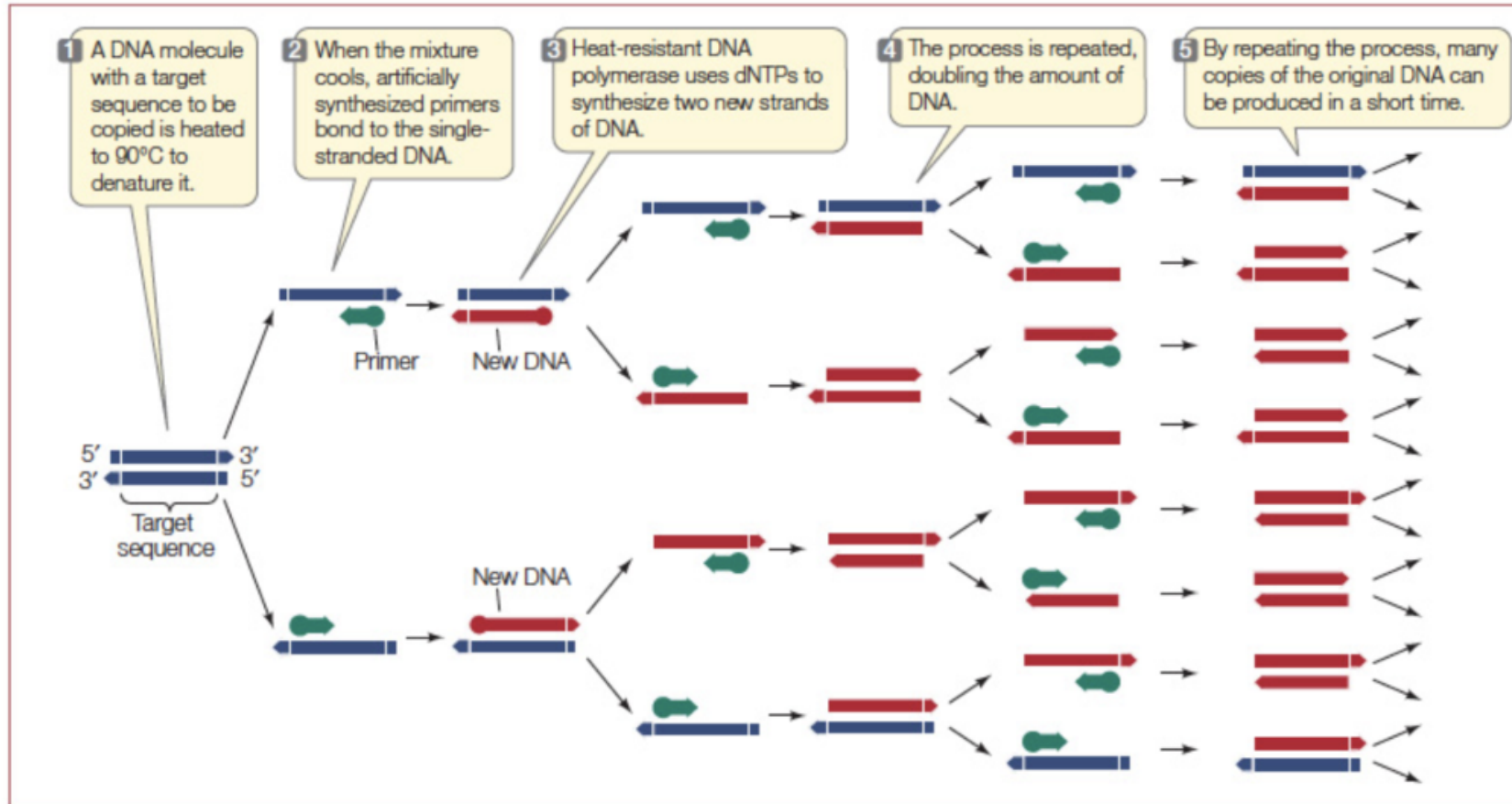
- Detection of viral genomes
  - Detects the formation of infectious viral particles
  - May miss very early infections
  - Performance in the field may vary (issues such as sample collection)
  - Two ways to do this: PCR Thermocycler or Isothermal PCR
- Detection of antibodies directed against the virus
  - Detects the immune response after infection
  - Interpretation of results may be complicated due to cross reactivity with other Corona viruses
  - Antibody testing is best for determining exposure at the population level

# Detecting the Corona Virus Genome

- Detecting genetic material using Polymerase Chain Reaction methodology (PCR)
  - Current test, developed in the mid-1980s
  - Uses a well understood and widely adopted technology
  - Traditionally done with a device called a “Thermocycler” (see next slide)
- Viral sequence published by the Chinese
- **If done correctly can be very accurate,**
  - **but sensitivity and specificity of current tests (as implemented in the field) are unknown especially in detecting early disease**

# Traditional Thermocycler Testing

From: <https://media.cheggcdn.com/media%2F521%2F5211db62-161f-4027-b1c3-54813815b66c%2FphpNpl0B1.png>



# Detection of the Corona Virus Genome

- Newly-developed technology uses isothermal PCR.
  - A variety of protocols exist
  - One example: <https://www.neb-online.de/en/pcr-and-dna-amplification/isothermal-amplification/>
  - Abbott Laboratories has an isothermal PCR Corona test that is FDA approved
- Benefits
  - Allows point of care testing in a physician's office
  - Instrumentation can be simpler and integrated with other non-PCR tests
  - Results are also available far quicker



# Detection of the Corona Virus Genome

- PCR tests, both traditional and isothermal, are relatively easy to develop given adequate sequence information (which China recently supplied)
- Development of PCR tests are within the technical capability of many laboratories at U.S. academic medical centers (as well as others globally)

# Detection of the Corona Virus Genome

- Reagent and equipment shortages have limited ability to ramp up
  - Hopefully, this will resolve in the next few weeks
  - **However a global bottleneck in supplies could be a major problem!**
- Downside: determines if the patient is currently infectious but not if the patient has been infected and has recovered.
  - Thus, not the most useful test in determining the prevalence of the virus in the population and the development of “herd immunity”
  - [Herd Immunity](#) (Wikipedia): “is a form of indirect protection from infectious disease that occurs when a large percentage of a population has become immune to an infection, whether through previous infections or vaccination, thereby providing a measure of protection for individuals who are not immune.”
  - Immunity in 40% to 70% of the population is needed to achieve herd immunity

# Corona Antibody Testing

- Detects individuals who have recovered from infection
  - Crucially needed to determine the level of immunity in the population including individuals who had asymptomatic infections
  - Without these test we cannot calculate how many asymptomatic infections were present in the population or the death rate
- Tests are becoming available but not yet at scale
  - can be readily scaled once reagents exist
- Test interpretation may prove challenging

# Predictive Value of Mass Screening

- Sensitivity is the ability of the test to detect individuals who have the disease (true positives)
- Specificity is the ability of the test to render a negative result in patients who do not have the disease (true negatives)

# Predictive Value of Mass Screening

- Assume the following:
  - A test that is both 99% sensitive and 99% specific
  - Used to screen a population of 1-million people
  - Where 10,000 (1%) have the disease and 990,000 do not.
- This means:
  - 9,900 true positives are identified, 100 true positives are missed
  - 9,900 false positives are identified
  - Thus the predictive value of a positive test is 50%
- Problem:
  - Possible waste of public health resources if based on the finding of a single test.
  - Traditional test protocols address this concern by using a rapid, but sensitive, screening test followed by more specific confirmatory test

# Can Labs Respond?

- Yes if:
  - workforce and resources redirected towards Corona testing
  - certain regulations are waved/relaxed
  - test supplies are adequate
- But:
  - workforce limitations exist and laboratory personnel may fall ill
  - may limit other types of laboratory tests
  - It is not just running the test! Bottle necks include:
    - Accessioning samples
    - Reporting results especially when samples come from sources that lack electronic interfaces to report results

# Social Distancing, Antivirals, Vaccines and Herd Immunity.

- Social Distancing: Bend the curve
- Antivirals: Attack the virus
- Vaccines: Induce immunity
- Herd Immunity: Allow the virus to spread in a controlled manner

# Social Distancing: Bend the Curve

- At best it may take a prolonged period that is unsustainable or may be unneeded (very controversial):
  - <https://www.imperial.ac.uk/media/imperial-college/medicine/sph/ide/gida-fellowships/Imperial-College-COVID19-Global-Impact-26-03-2020.pdf>
  - <https://off-guardian.org/2020/03/24/12-experts-questioning-the-coronavirus-panic>
  - <https://off-guardian.org/2020/03/28/10-more-experts-criticising-the-coronavirus-panic/>
- Unless very strictly implemented infections may still increase
  - <https://www.visualcapitalist.com/the-math-behind-social-distancing/>
- Assumes no significant animal reservoir



# Social Distancing: Bend the Curve

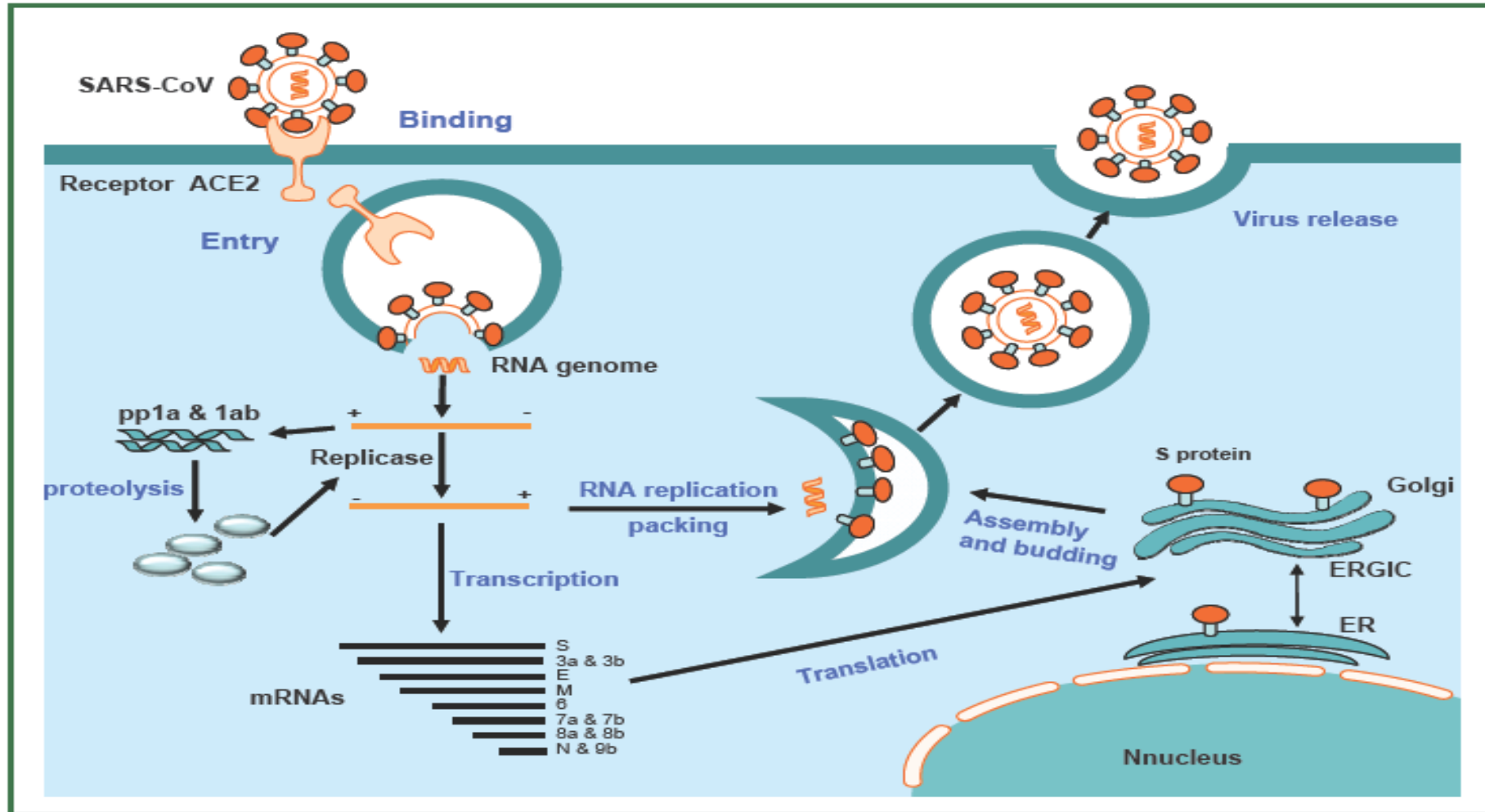
- Infected individuals will remain or possibly cross borders
  - Exponential growth will reemerge
- Delays the development of herd immunity through infection
- May not be able to achieve an adequate level of containment while maintaining vital economic functions
- Will have a disproportionate impact on necessary workers
- Rapid development of new antivirals and vaccines are critical for this current strategy to succeed!

# Antivirals

- Both current and experimental drugs show some promise
  - Approaches to drug development discussed on next slide
- Must collapse the time of clinical trials, this will mean some loss of statistical rigor, but we have no choice
- A reasonably effective drug that is nationally available now will save more lives than a better drug later
  - Follow current Hydroxychloroquine studies closely
- A drug that reduces hospitalization and ventilator rates is effective!

# Corona Virus Life Cycle

From: <https://virushostinteractions.wordpress.com/2015/02/10/nidoviruses/>



# Antiviral Production and Delivery

- Small molecule drug production will vary depending on the pathways needed to synthesize them
- Nucleic acid based drugs and vaccines maybe able to be produced very rapidly
- Monoclonal antibodies may be scaled rapidly depending on the degree of customization
- Non-monoclonal antibody protein biologics may be very time consuming to make
- Route of delivery (i.e., IV versus by mouth) matters, as does dosing schedule and cold supply chain

# Vaccines

- 12-18 months away if all goes perfectly
- Not only need to be tested but production must be scaled nationally
  - may be much easier with vaccines based on nucleic acid technologies
- Is there an example of a prior Corona virus vaccine in humans?
- How protective are the antibodies the vaccine produces and how long do they last?
- Study design issues include end points and negative control arms
- What if we nationally implement an ineffective vaccine?

# Herd Immunity

See: [https://en.wikipedia.org/wiki/Herd\\_immunity](https://en.wikipedia.org/wiki/Herd_immunity)

- Achieved by immunization or letting the disease spread through the population until immunity blocks exponential growth
  - Let  $R$  = reproduction number which is the number of people that an infected person infects. Then the proportion of the population needed to achieve herd immunity:
    - $PH = 1 - (1/R)$
    - For example for  $R=2$ ,  $PH = 50\%$
    - $PH$  probably around 70% for current epidemic
  - Anecdotal reports of second infections
- May be combined with mitigation by isolation and/or pharmaceutical prophylaxis of most vulnerable populations

# Factors Influencing Death Rate

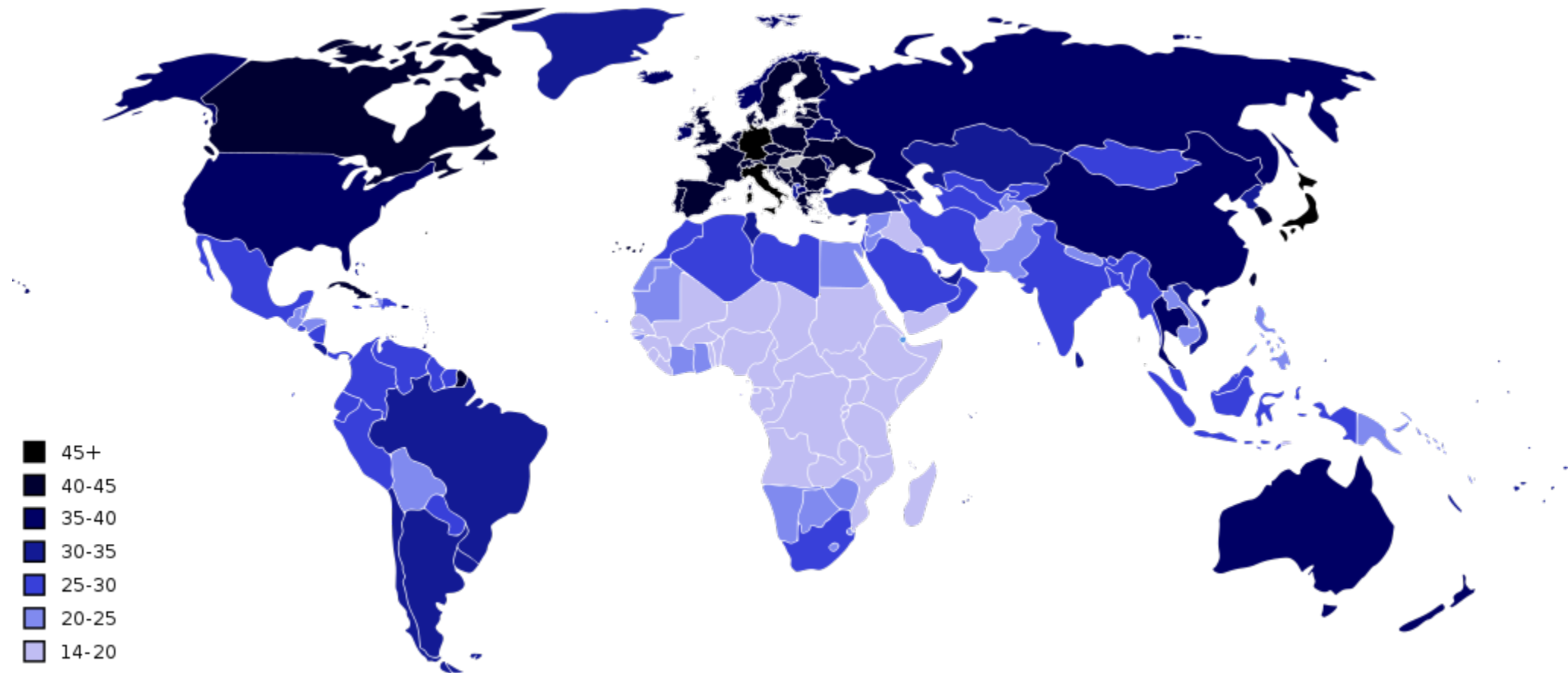
- Includes climate, sources of exposure, adequacy of the healthcare system and age/comorbidity
- Much will depend on whether the healthcare system breaks down under stress
- Age is a major factor
  - China and the US median age is about 38
  - Mexico is 28 and much of Africa is under 25
  - Countries with lower median ages **may** be able to achieve useful levels of herd immunity without many deaths

# Median Age by Country

From:

[https://en.wikipedia.org/wiki/List\\_of\\_countries\\_by\\_median\\_age#/media/File:Median\\_age\\_by\\_country,\\_2016.svg](https://en.wikipedia.org/wiki/List_of_countries_by_median_age#/media/File:Median_age_by_country,_2016.svg)

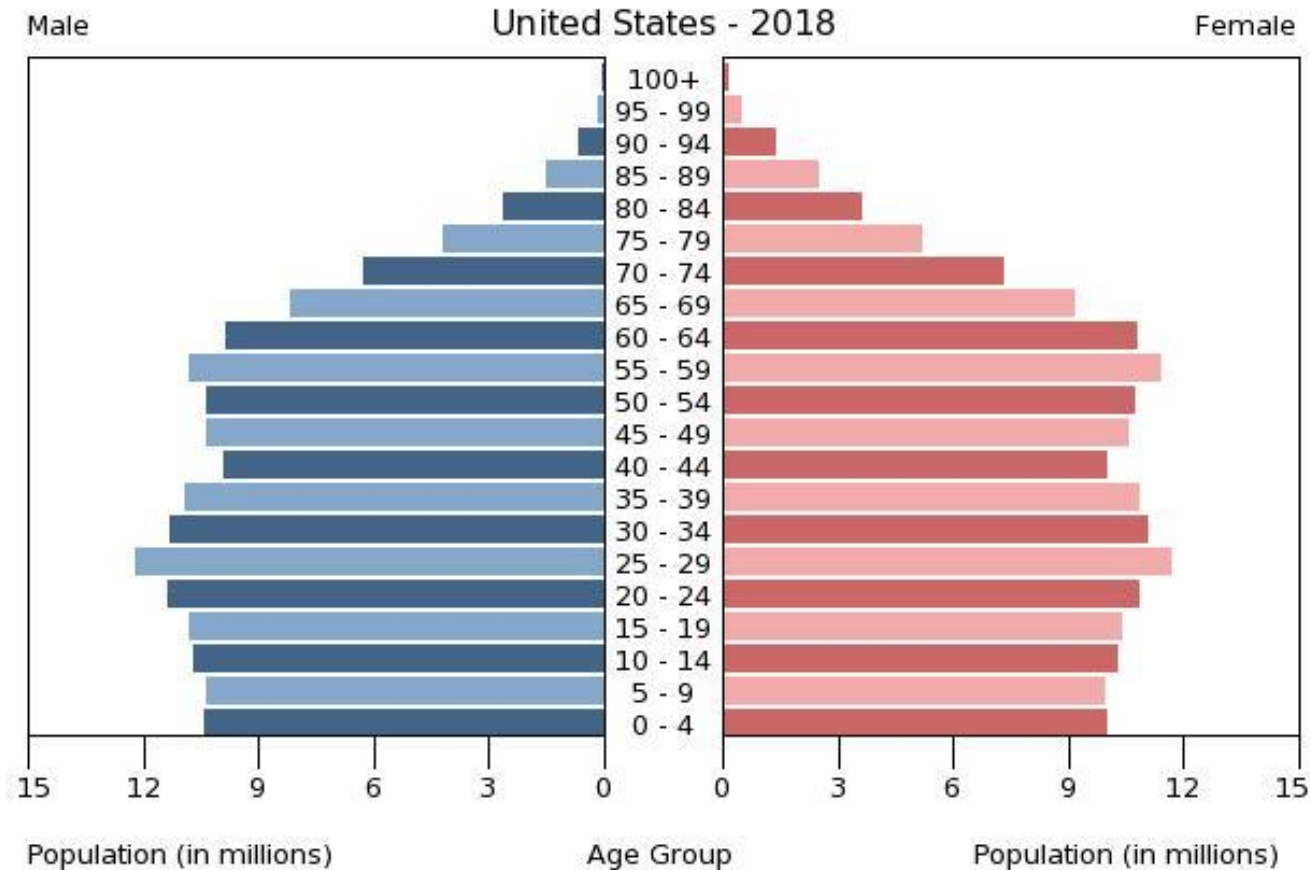
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# Current U.S. population distribution:

[https://www.indexmundi.com/united\\_states/age\\_structure.html](https://www.indexmundi.com/united_states/age_structure.html)



# So How to CorVexit in the U.S.?

- A strawman when we have achieved adequate national testing capacity in the spring (and may also see seasonal reduction effects):
  - Consider selectively relaxing quarantines
  - Continue isolation of major geographic hot spots
  - Continue isolation of elderly and other high-risk patient populations
- Greatly ramp up public health efforts to track contacts
- Consider prophylactic treatment of high-risk patients with antivirals especially if current drugs can be repurposed
  - Continue clinical trials as fast as possible on all reasonable candidates
- Otherwise allow herd immunity to spread
- **But there is no silver bullet!**