IMMUNISATION COALITION

Recent pandemics and informed predictions

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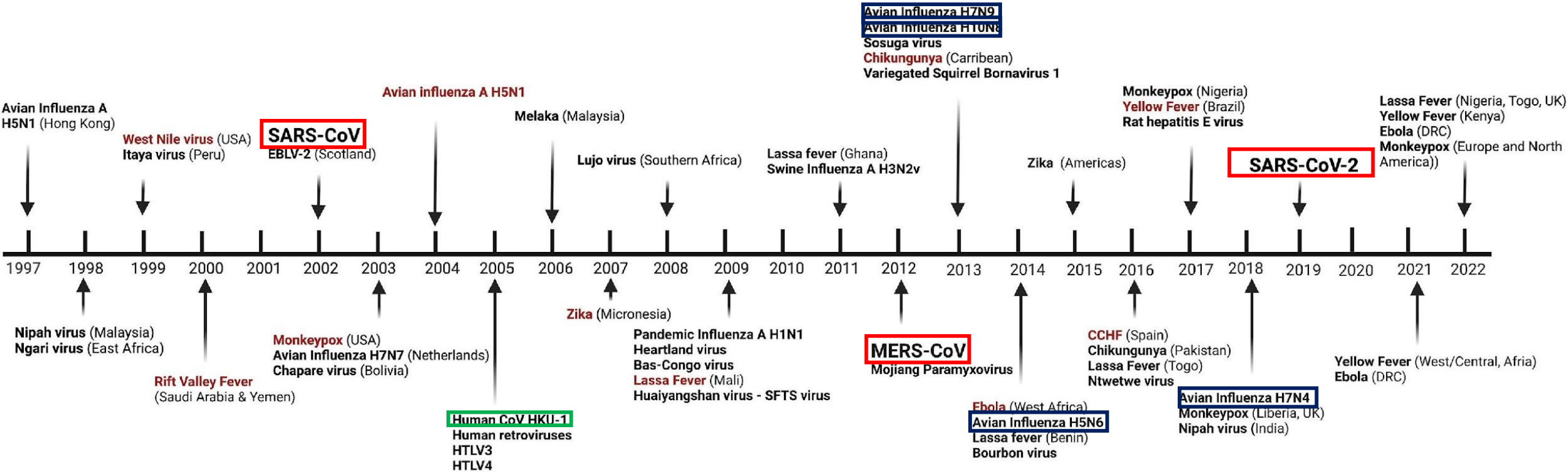
Recent pandemics #1

- 1918 influenza pandemic
- 2019 COVID-19
- Ebola outbreak/epidemics
- HIV pandemic
- Two of these were caused by respiratory viruses while two were not transmitted via a respiratory route.
  - None of these viral infections were easily contained, although there was most success with Ebola.
- All of these were zoonotic.

Recent pandemics epidemics, outbreaks and identification of human pathogens



SARS-CoV, MERS-CoV, SARS-CoV-2 were new to humans
HKU-1 was not new in 2005, but was newly identified.

Keusch et al, PNAS, 2022

Prediction #1-Next pandemic virus will be a zoonotic respiratory virus, with a caveat.

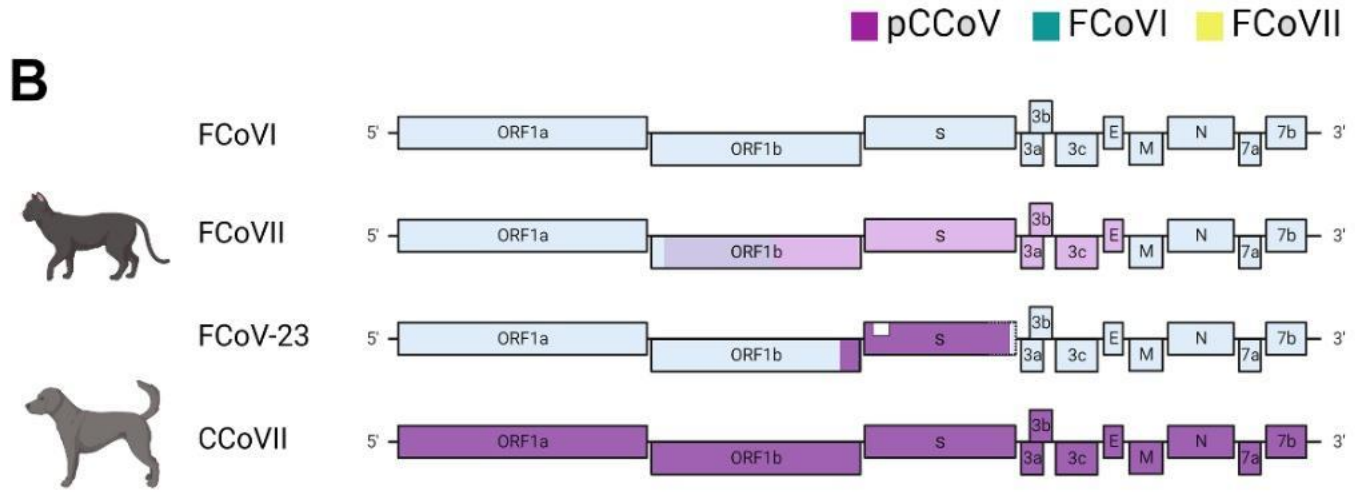
- Humans will be immunologically naïve to the virus.
- Virus needs to be able to efficiently transmit from human to human.
  - This was key difference in between SARS-CoV and SARS-CoV-2 since both use ACE2 as a receptor but only SARS-CoV-2 efficiently infected the upper airway (or was able to transmit from the upper airway).
- The caveat is that there may be surprises still.
  - Two new feline/canine coronaviruses were recently identified, with novel features.

Novel canine/feline coronaviruses

- One was identified in children in Malaysia with respiratory illness
  - Contained genetic information from canine, feline and swine CoV.
  - These viruses all use the same receptor and can fairly easily cross species.
  - Never found in Nature
  - No evidence for interhuman transmission
- Second novel CoV was identified in cats in Cyprus.
  - Feline CoV is enteric pathogen that is easily transmitted from cat to cat.
  - Occasionally, mutations occur in a persistently infected host which results in a change in cellular tropism from epithelial cells to macrophages (“feline infectious peritonitis virus” FIPV).
  - This version of FIPV is highly lethal, but does not transmit from cat to cat.

Novel canine/feline coronaviruses #2

- Recently, an outbreak of FIPV occurred on Cyprus. This is not supposed to occur because FIPV is sporadic.



This virus is FIPV with a deleted version of a specific canine CoV S protein.
Thus, this virus is not completely new, but is has gained the ability to transmit via recombination. The virus is highly virulent and transmissible.

Prediction #2-Surveillance will be critical for identifying potential pandemic viruses but will be controversial.

- Surveillance is critical to identify possibilities.
- How will surveillance work?
  - Surveillance of wildlife at human-wildlife interface?
  - Definition of high risk areas.
  - Surveillance for antibody responses to high risk pathogens in specific locations of high zoonotic cross over?
  - Surveillance of patients with pneumonia in high risk areas?

Prediction #2-Surveillance will be critical for identifying potential pandemic viruses but will be controversial.

- Surveillance has to be focused. Otherwise, there will be information overload.
  - What will we do with information? Several studies prior to 2019 demonstrated the presence of bat CoVs able to infect human cells.
  - In retrospect, what could we have done with this information? Vaccine development? Development of anti-viral therapies? Unlikely that either approach would have received monetary support prior to 2019.
  - Development of MERS-CoV vaccine did not receive adequate funding prior to the pandemic.
- There are also those who believe that surveillance is bad because it potentially releases human pathogens from sequestered reservoirs into human populations.
  - High biosafety laboratories used for these studies. Contrary to statements made in parts of the press and by several individuals, these are safe.
  - Key will be to make sure that users adhere to biosafety and biosecurity guidelines.

Prediction #3-We will know more about the agent causing the next pandemic than we think

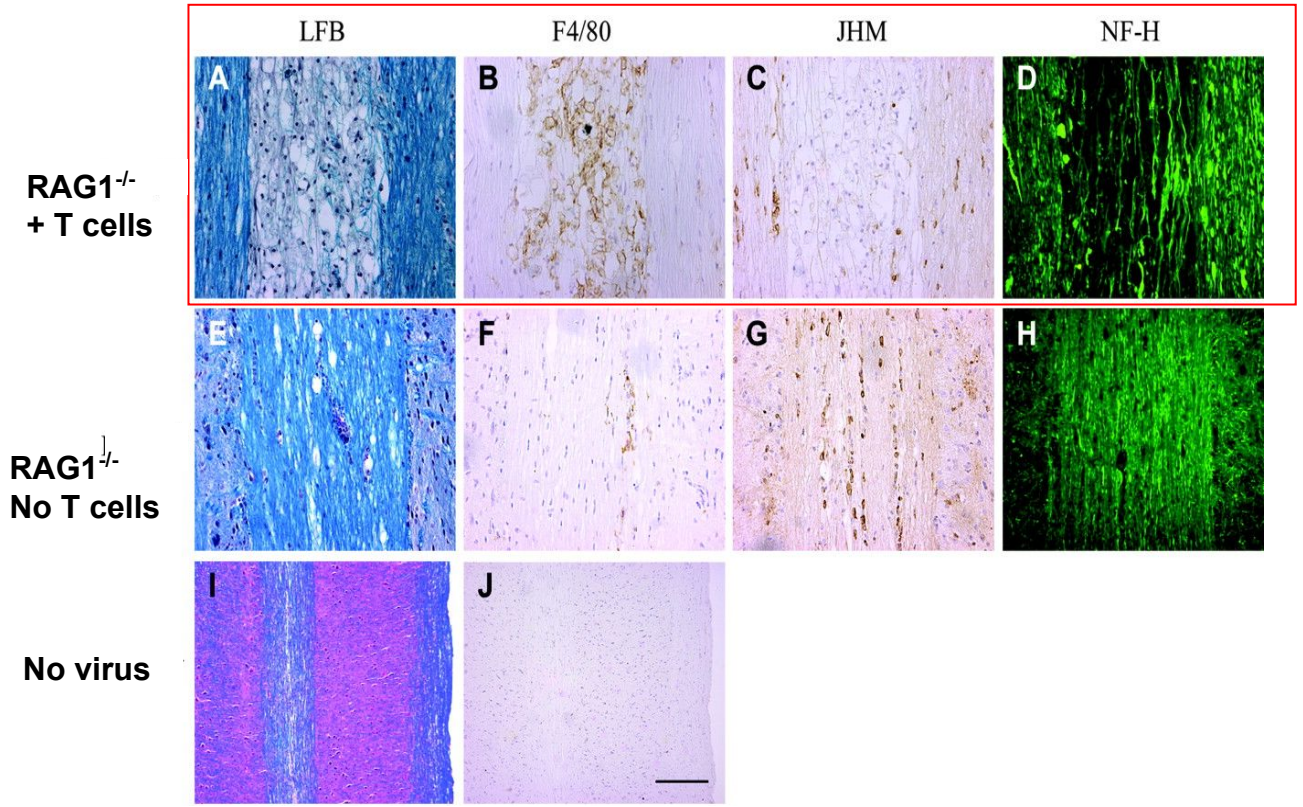
- In beginning of pandemic, there was fear of the unknown, especially given the 1-2% mortality.
- However, even though the coronavirus research community was tiny, much was known about the replication strategy of the virus.
- Reverse genetics systems were well established.
- Potential targets for anti-viral therapy were known.
  - Protease inhibitors had been developed for FIPV. These reduced mortality from 100% to 50%.

Prediction #3-We will know more about the agent causing the next pandemic than we think

- Vaccines had been developed for coronaviruses that caused disease in farm and companion animals.
  - Many of these were ineffective.
  - Some were deleterious. Under research settings, vaccination with the FIPV S protein resulted in enhanced disease because of change in tropism to macrophages.
  - This raised concerns about antibody disease enhancement at the beginning of the pandemic.
- We knew the major target for the neutralizing antibody response.
- We knew about the target for the T cell response in humans and experimentally infected laboratory animals.
- We knew that coronaviruses caused immunopathological disease.

Immunopathology in a murine CoV infection.

Virus clearance and concomitant myelin destruction and axonal damage



Prediction #3-We will know more about the agent causing the next pandemic than we think

- We knew that RNA viruses lack proofreading activity so were present as quasispecies swarms in any individual host.
  - This occurred because viral RNA-dependent RNA polymerases lack proofreading activity.
  - This was true even for coronaviruses, which encode a protein with proofreading activity (nsp4). Error rate is still substantially higher than host or DNA virus polymerases.
  - We knew that these viruses readily mutated, but we did not know the level to which SARS-CoV-2 would mutate, initially to enhance replication and transmission and later to evade the host immune response.
- We knew how to monitor changes in virus sequence.
  - This was based in part on experience with influenza virus evolution
  - Some of these changes enhanced the ability of the virus to enter cells.
  - The basis of many other changes is still an area of investigation.

Prediction #4-We will make mistakes

- In the COVID-19 pandemic, several types of mistakes were made, many only apparent in retrospect.
- Some were medical in nature.
  - Pathophysiology, at least at early times after infection, was different from other respiratory infections.
  - Use of ventilators early in the pandemic created problems.
- Some therapeutic interventions were attempted without supportive data.
  - Most highly publicized examples were hydroxychloroquine and ivermectin.
  - Ivermectin useful for treating parasitic infections (e.g., strongyloidiasis, Onchocerciasis), scabies, etc.
  - No proven efficacy in viral infections.
  - Even as of January 2024, ivermectin is recommended for therapy by some physicians.

Prediction #4-We will make mistakes-hydroxychloroquine

- Pre-pandemic in vitro studies showed that chloroquine and hydroxychloroquine inhibited coronavirus entry, but only when virus entered cells via the endosomal pathway.
- No evidence for efficacy in coronavirus-infected animals (prepandemic).
- In pandemic, hydroxychloroquine was used for therapy, with change of rationale now including anti-inflammatory effects.
- Became politicized.
- Large studies showed that HCQ was not beneficial and potentially harmful.

Prediction #4-We will make mistakes in communication

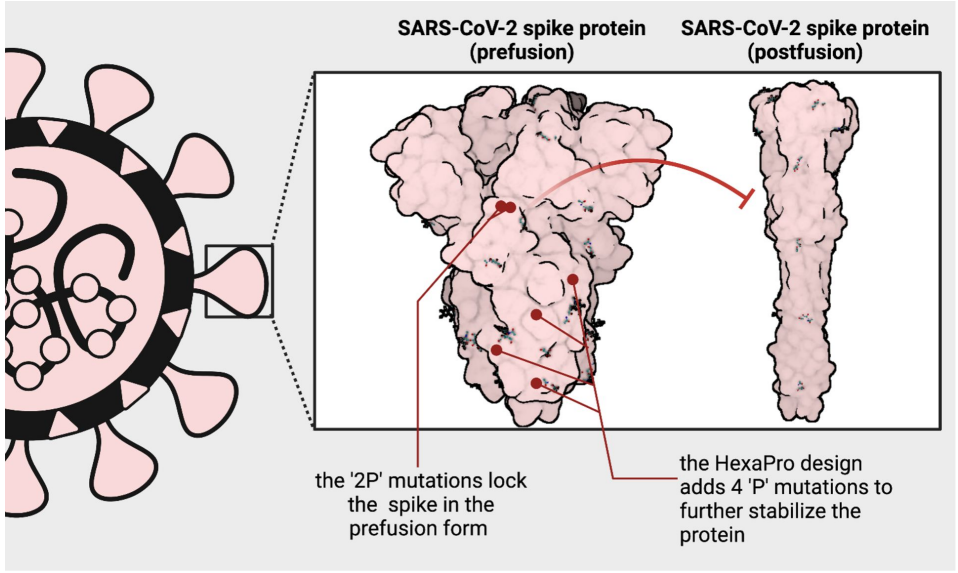
- Communication to broad public was often difficult; errors were made.
- Many of these errors occurred because new information was available on almost a daily basis.
  - For example, initially, pregnancy was not considered a risk factor for worse COVID-19.
  - Then it became apparent that fetuses were not infected, but the placenta could be. Pregnancy outcomes were worse.
  - Finally it was realized that pregnancy itself was a risk factor for worse outcomes, including ICU admission and death.

Prediction #4-We will make mistakes in communication

- Other errors had multifactorial bases, such as messaging on use of masks.
  - Originally, masks were considered unnecessary, since spread was considered to be by contact or large droplets.
  - Based in part on studies of infection with respiratory syncytial virus and other respiratory virus infections.
  - It became apparent that virus spread in small droplets.
  - In addition, at the beginning of the pandemic, there was a mask shortage. This was part of the basis for not recommending mask usage.
  - In retrospect, information about mask usage could have been more nuanced.
- School closures are a second example.
  - Appeared necessary to stem pandemic early on.
  - However, it became apparent that children did not transmit SARS-CoV-2, but schools remained closed for longer than necessary in many places.
  - Some children are still suffering from years of lost education.

Prediction #5-We will make effective uses of scientific advances

- Most obvious example from COVID-19 is vaccine development.
  - mRNA vaccines were possible because of advances in:
  - RNA technology
  - vaccine formulation (nanoparticles, lipid nanoparticles)
  - Adjuvants (e.g., Matrix-M used in Novavax vaccine (S protein-based).
  - SARS-CoV-2 and RSV vaccine development also made use of development of pre-fusion surface glycoprotein constructs.
- Vaccine development was enhanced by these advances but they were not necessary.



Biorender, Vanderbilt Institute for Infection, Immunology and Inflammation

Prediction #5-We will make effective uses of scientific advances

- Advances partly derived from COVID-19 pandemic will used in the future.
- 1. Correlates of protection better (not perfectly) understood.
- 2. Maturation of antibody response (memory B cells vs. plasma cells)
- 3. Importance of non neutralizing antibody titers in protection
  - T cells
  - Non neutralizing antibody function
  - Memory innate cell functions.
- 4. Nuances of antigenic imprinting.
- 5. Use of wastewater to monitor virus spread, especially when virus testing is diminished.
- 6. Use of human challenge trials.

Prediction #6-A future pandemic will bring out the opportunists.

- Disagreements about best approaches are important because they often lead to better approaches but become intractable when they end up as political discussions.
- Individuals and groups will use fear as tool to gain power and money.
- Power: “Florida State Surgeon General Calls for Halt in the Use of COVID-19 mRNA Vaccines” because of ”the risk that DNA integrated into sperm or egg gametes could be passed onto offspring of mRNA COVID-19 vaccine recipients.”
- Money: Anti-vaccination websites sold unproven therapies such as ivermectin, which led to profits.
- These claims are often hard to refute because of distrust of healthcare authorities plus desire for an easy and quick remedy.

Prediction #7- There will be better availability of vaccines and therapies worldwide.

- Countries like India were able to produce large amounts of vaccines and anti-viral therapies, increasing accessibility of cheaper vaccines worldwide.
- This may ameliorate some of the global inequalities in terms of vaccine and to a lesser extent antiviral therapies.
- Organizations such as CEPI are stockpiling vaccines.
  - This has limitations because vaccines expire and we do not know what will actually be needed against the next pathogen.
  - We also learned that vaccines can be produced very rapidly and safely.
- However, it will be critical to overcome vaccine hesitancy.

Prediction #8- There will be cheap and readily available antiviral therapies (aspirational)

- An oral anti-viral therapy would be more readily accepted by general populations.
- Paxlovid is highy effective, but too expensive, especially in low income countries.
- For CoV, would protease inhibitors be effective against a broad range of coronaviruses?
- Stockpiling these would need to overcome problems with expiration dates.

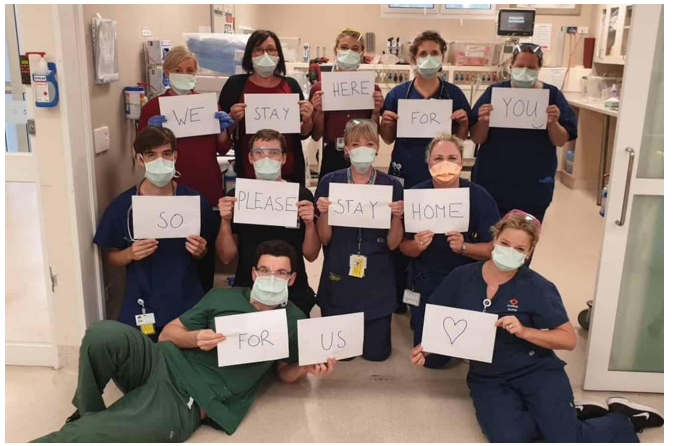
Prediction #9-There will be less ethnic, racial and economic disparities in access to vaccines and therapy (aspirational)

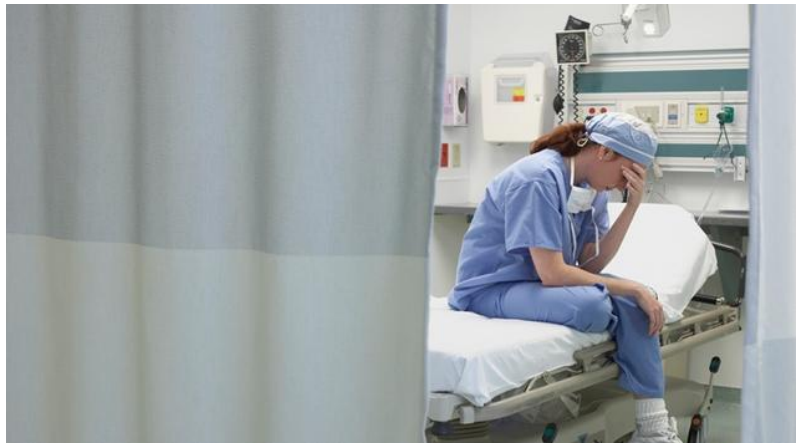
- There were differences in access to vaccines and therapies, depending on ethnic, racial and economic factors.
- There were also differences in acceptability to different communities, as least in the US.
  - African-American communities were distrustful of the healthcare system for multiple reasons (poor access to healthcare, conscious and unconscious bias, history fo clinical trials without appropriate consent, etc.
- However, many of these disparities in vaccine uptake decreased over the course of the pandemic, in part because white Americans decreased vaccine uptake.
- Uptake in aged populations was not a factor in the US, but was in countries such as China.
- These factors are independent of disparities in access to mRNA vaccines and requirements for cold chains.

Prediction #10- There will be human altruism.

- Healthcare workers, including physicians, nurse, medical assistants, ambulance drivers, cafeteria workers, etc.
  - Some were poorly paid
- As critically, those who provided basic services-police, fire fighters, custodians, etc.
- In research laboratories, animal facility personnel,

Prediction #10- There will be human altruism.





Prediction #11-If the next pandemic is caused by a CoV, it will not be a sarbecovirus

- MERS-CoV, the cause of the Middle East Respiratory Syndrome coronavirus is a camel virus with little interhuman transmission except in hospital and perhaps household settings.
- MERS-CoV could become more transmissible.
- However, from the COVID-19 pandemic we learned that it is not the known CoV (such as SARS-CoV) that are a problem, but rather the unknown CoV.
- Thus MERS-like CoV, probably in bats, camelids and perhaps other animals must be high on the list of pathogens that require vigilance.
- An additional concern is that some MERS-like CoV can use ACE2 as receptor

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