# COVID-19 Vaccine Development— Where are we now?

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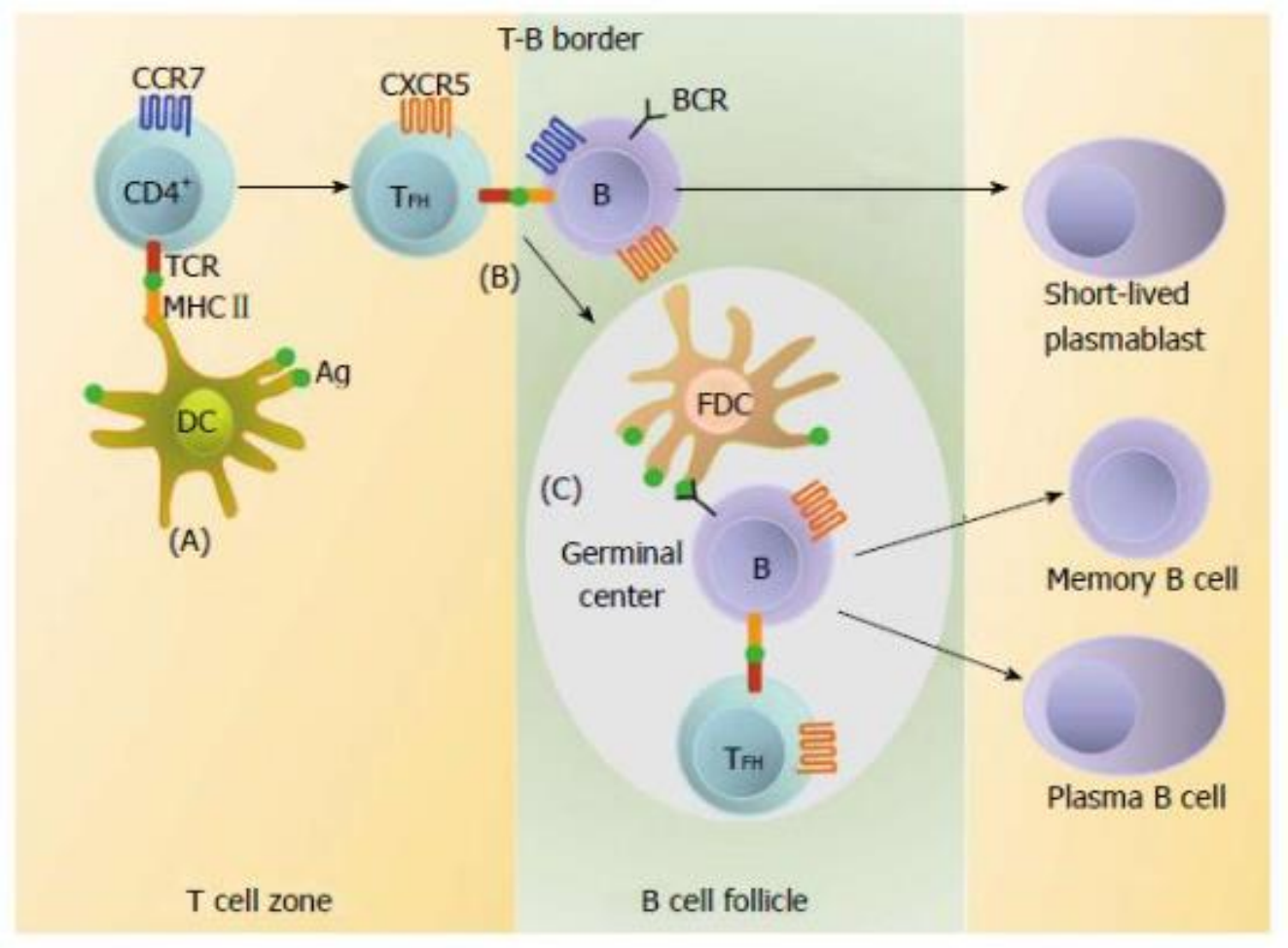
# Disclosures

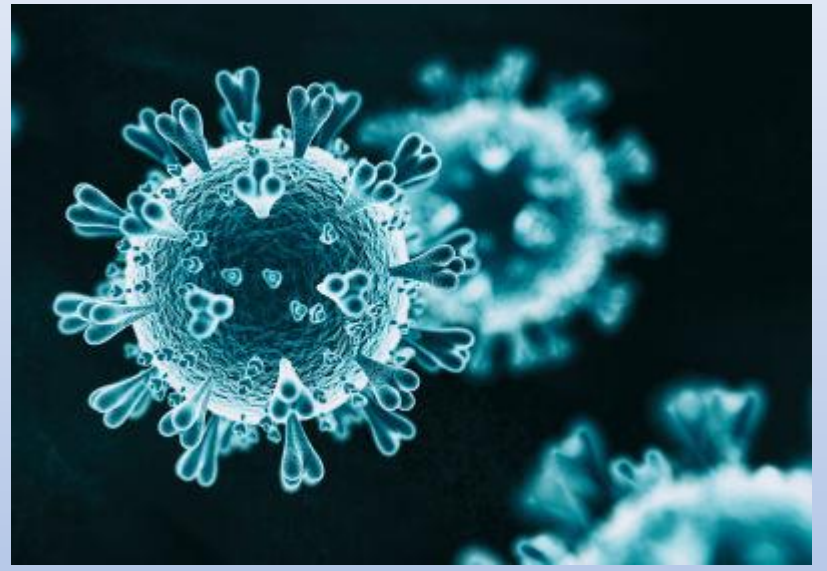
- None

# Learning Ojectives

- Discuss the pros and cons of the different types of vaccines.
- Discuss what some of the risks of a vaccine might be beyond lack of efficacy.
- Discuss what has been presented so far in a peer reviewed journals.
- Discuss when vaccines may be available and how truly unprecedented this rate of development is.

# Immunology Quick Review



Parodi C, Bandano MN, Galassi N, et al. World Journal Hematology 2014;3(4):118-127

# Immune responses to Coronaviruses

- Neutralizing antibodies to seasonal and SARS-CoV-1 have been shown to wane with time.

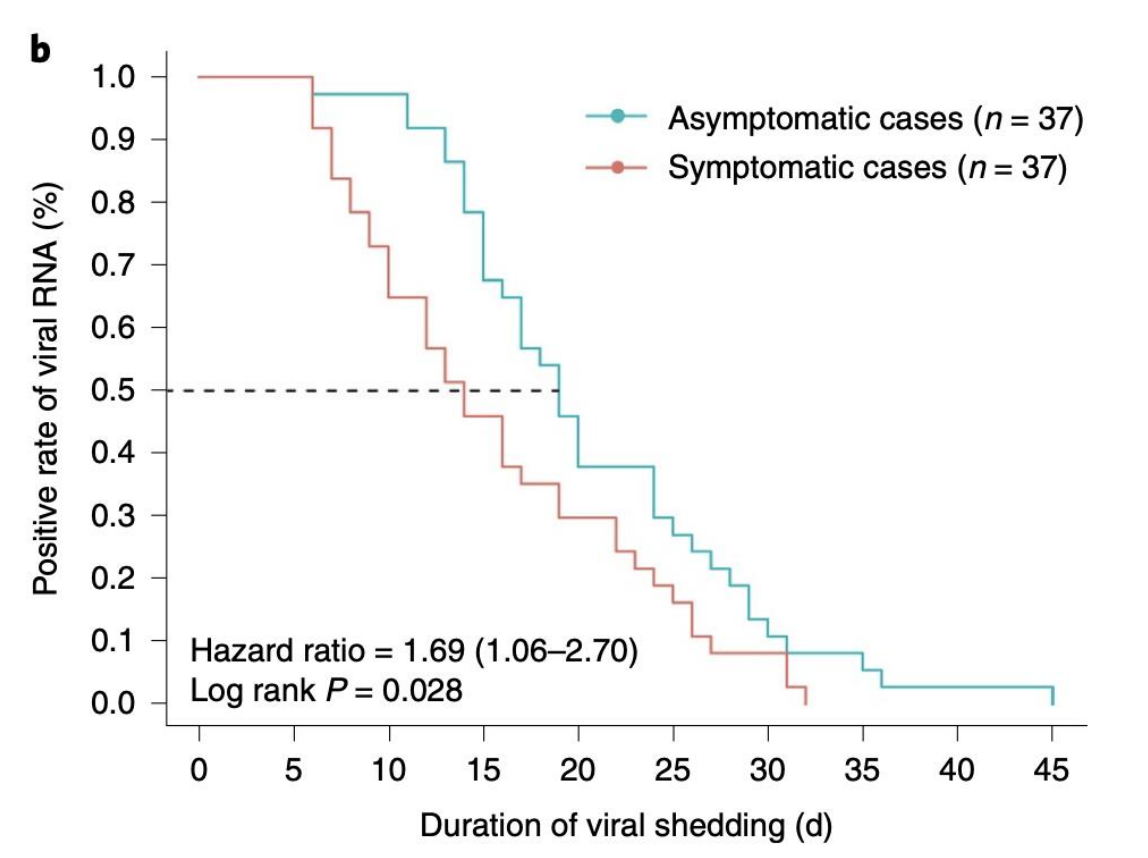
  Callow KA, Parry HF, Sergeant M, Tyrrell DAJ. Epidemiol Infect 1990;105:435-446.

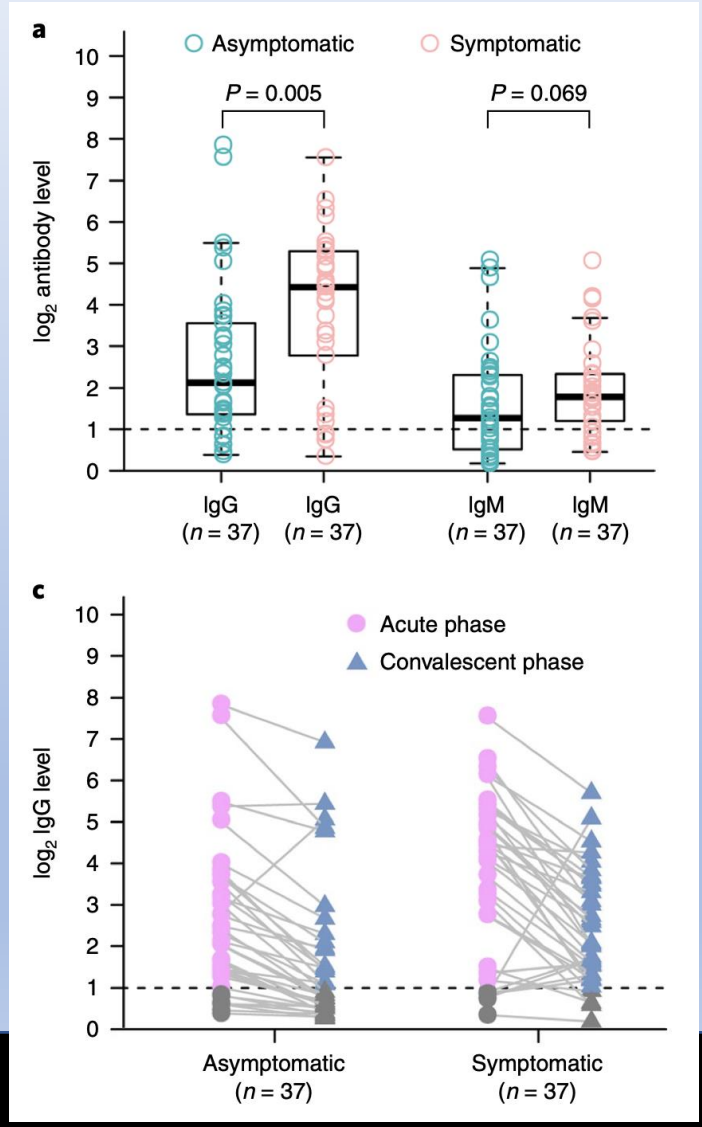
  Tang F, Quan Y, Xin ZT, et al. J Immunology 2011;186:7264-726.

- Neutralizing antibodies to MERS have been shown to be higher in patients with severe disease than those with mild disease.

  Choe PG, Perera RAPM, Park WB, et al. Emerg Infect Dis 2017;23(7):1079-1084

# Immune Responses SARS-CoV-2

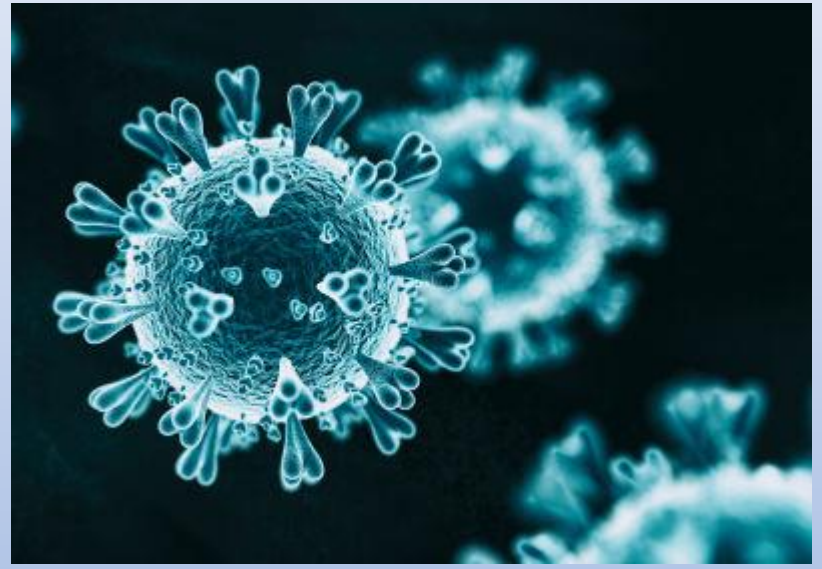



Long QX, Tang XJ, Shi QL, et al. Nature Med 2020.
https://www.nature.com/articles/s41591-020-0965-6.pdf

# Vaccine Models in Development

- DNA Based
- RNA Based
- Subunit
- Vector Based
- Killed virus
- Live attenuated



# DNA Based Vaccines

- No currently licensed vaccines
- Uses DNA coding for antigen(s) of interest (COVID-19 Spike Protein) usually with a promoter region attached.
- Challenges
  - Uptake by antigen presenting cells (Dendritic cells)
  - Concern for possible integration into host DNA
- Advantages
  - Adaptable to changes in viral antigens
  - DNA Stable
- Status
  - 12 in development

Rauch S, Jasny E, Schmidt KE, Petsch B. Frontiers in Immunology 2018;9:1-24
https://milken-institute-covid-19-tracker.webflow.io/#vaccines_intro

# RNA Based Vaccines

- No currently licensed vaccines
- Uses mRNA or self-replicating RNA to express antigen(s) of interest.
- Challenges
  - Uptake by antigen presenting cells (Dendritic Cells)
  - RNAses
- Advantages
  - Adaptable to changes in viral antigens
  - No concerns for integration into host DNA
- Status
  - 21 in development

Rauch S, Jasny E, Schmidt KE, Petsch B. Frontiers in Immunology 2018;9:1-24
https://milken-institute-covid-19-tracker.webflow.io/#vaccines_intro

# Subunit vaccines

- Several licensed vaccines:  Hepatitis B, Influenza, tetanus, Shingrix
- Antigen of interest is given with adjuvant (Alum), or a conjugate (additional protein to help uptake into dendritic cells) or “Viral like particles.”
- Challenges
  - Often not very immunogenic
- Advantages
  - Safe and well tolerated
- Status
  - 65 in development

Vetter V, Denizer G, Friedlant LR, et al.  Ann Med 2018;50(2):110-120

https://milken-institute-covid-19-tracker.webflow.io/#vaccines_intro

# Vector Based Vaccines

- One licensed vaccine:  Ervebo (Ebola virus vaccine)
- Uses a replication deficient virus (i.e. adenovirus) to carry the antigens of interest.
- Challenges
  - Pre-existing immunity to the viral vectors can prevent devolvement of new immunity
  - Viral vectors are genetically modified infectious organisms
- Advantages
  - Uptake by antigen presenting cells (Dendritic cells)
- Status
  - 35 in development

Rauch S, Jasny E, Schmidt KE, Petsch B.  Frontiers in Immunology 2018;9:1-24
https://milken-institute-covid-19-tracker.webflow.io/#vaccines_intro

# Killed Virus Vaccines

- Several licensed vaccines:  Hepatitis A, IPV, Rabies, whole cell pertussis
- Killed virus is taken up like a live organism mimicking natural immune response
- Challenges
  - Immune reactions
  - Less immunogenic and repeated vaccination required
- Advantages
  - Fairly straight forward production process
  - Multiple antigens present
- Status
  - 9 in development

Vetter V, Denizer G, Friedlant LR, et al.  Ann Med 2018;50(2):110-120
https://milken-institute-covid-19-tracker.webflow.io/#vaccines_intro

# Live Attenuated Vaccines

- Several licensed vaccines:  MMR, Oral Polio, Zostavax
- Causes mild form of the actual infection.
- Challenges
  - Can revert to a more virulent form
  - Complicated to make
  - Can’t given to persons with immunocompromising conditions
- Advantages
  - Multiple antigens present
  - Very effective with long last immunity (and can promote herd immunity)
- Status
  - 3 in development

Vetter V, Denizer G, Friedlant LR, et al.  Ann Med 2018;50(2):110-120
https://milken-institute-covid-19-tracker.webflow.io/#vaccines_intro

# Concerns

- Studies with MERS and SARS-CoV-1 vaccine in animal models showed “disease enhancement” with exposure to the virus after vaccination.

  Agrawal AS, Tao X, Algaissi A, et al. Hum Vacc Immunother 2016;12(9):2351-2356

  Wu SC. Biotechnology Journal 2020;2000147

  Lambert PH, Ambrosino DM, Andersen SR. Vaccine 2020;38:4783-4791

  De Alwis R, Chen S, Gan ES, Ooi EE. EBioMedicine 2020;55:102768

- Prior RSV vaccination in infants led to higher rates of PNA and hospitalization due to an over-exuberant immune response.

  Kapikian AZ, Mitchell RH, Chanock RM. Am J Epidemol 1969;89(4):405-421.

  Kim HW, Canchola JG, Brandt CD. Am J Epidemiol 1969;88(4):422-434.

# Vaccine Disease Enhancement

**Table 1**
Summary of published animal studies reporting protective and immunopathology phenotypes following immunization with various SARS-CoV and MERS vaccines.

| Virus | Animal | Vaccine type | Vaccination | Protective[a] | Immuno-pathology[b] | Ref. |
|---|---|---|---|---|---|---|
| MERS-CoV | Mice | [c]WIV | No Adjuvant | Yes | Yes | [57] |
| | | | Alum | Yes | Yes | [57] |
| | | | MF59 | Yes | Yes | [57] |
| | | Adenovirus Vector | S1 | Yes | Yes | [63] |
| | | | S1 + CD40L | Yes | No | [63] |
| SARS-CoV | Mice | [c]WIV | No Adjuvant | Yes | Yes | [55,58,56] |
| | | | Alum | Yes | Yes | [55,58 [53], |
| | | | TLR agonist | Yes | [d]Mild | [58] |
| | | | delta inulin adjuvant | Yes | No | [56] |
| | | | No Adjuvant – Aged Mice | Partial | Yes | [53] |
| | | | Alum – Aged Mice | Partial | Yes | [53] |
| | | [e]VEE Vector | S protein | | | |
| | | | Young mice | Yes | No | [60] |
| | | | Aged mice | Partial | No | [60] |
| | | | N protein | | | |
| | | | Young mice | No | Yes | [60] |
| | | | Aged mice | No | Yes | [60] |
| | | | S + N Protein | | | |
| | | | Young mice | Yes | [d]Mild | [60] |
| | | | Old mice | No | [d]Mild | [60] |
| | | [f]VV Vector | S Protein | Yes | No | [76] |
| | | | N Protein | No | Yes | [76] |
| | | | S + N Protein | Yes | Yes | [76] |
| | | [g]VLP | No Adjuvant | Yes | Yes | [55,77] |
| | | | Alum | Yes | Yes | [55] [77] |
| | | Subunit | S Protein | | | |
| | | | No Adjuvant | Yes | Yes | [55,56] |
| | | | Alum | Yes | Yes | [55,56] |
| | | | delta inulin adjuvant | Yes | No | [56] |
| | | | TLR agonist | Yes | No | [59] |
| | | | S1 RBD | | | |
| | | | [h]FCA Adjuvant | Yes | No | [52] |
| | Ferret | [c]WIV | No adjuvant | Yes | Yes | [78] |
| | | | Alum | Yes | Yes | [78] |
| | | [i]Ad Vector | S + N protein | | | |
| | | | Intra-nasal | Yes | Yes | [78] |
| | | | Intra-muscular | Yes | Yes | [78] |
| | | [j]MVA Vector | S protein | No | Yes | [54] |
| | Hamster | [k]LAV | | Yes | [d]Mild | [79] |
| | | [c]WIV | No Adjuvant | Yes | [d]Mild | [80] |
| | | | AS01 | Yes | [d]Mild | [80] |
| | | Subunit | S protein trimer | | | |
| | | | No Adjuvant | Yes | No | [81] |
| | | | Alum | Yes | No | [81] |
| | NHP | [j]MVA Vector | S protein | Yes | Yes | [41] |

De Alwis R, Chen S, Gan ES, Ooi EE. EBioMedicine 2020;55:102768

# Results so Far

- DNA vaccine targeting the Spike Protein.
- Based on prior work on a DNA vaccine targeting the MERS spike protein.
- Vaccine was effective in creating neutralizing antibodies and T-cell responses in both mice and Guinea Pigs.
- Mice and Guinea Pigs were not challenged with virus.

Smith TRF, Patel A, Ramos S, et al. https://www.nature.com/articles/s41467-020-16505-0

# Results so Far

- Adenovirus Vector Vaccine
- Evaluated safety and immunogenicity in 195 *humans*
- Generally mild adverse reactions seen in 75 – 83% participants.
- Both neutralizing antibodies and T-cell responses were generate.  T-cell responses started to decline by day 28.

Zhu FC, Li YH, Guan XHm eta.  https://www.thelancet.com/action/showPdf?pii=S0140-6736%2820%2931208-3

# Results so Far

- Whole inactivated virus vaccine
- Two different doses of the vaccine given to rhesus macaques (n = 4 for both vaccine doses) or sham (n = 4) or saline (n = 4).
- Neutralizing Ab produced in both vaccine groups
- Macaques exposed to COVID-19 virus
  - Vaccinated macaques developed none or only mild disease
    - High dose macaques had no detectable virus after day 7
    - Low dose macaques had viral blips after day 7
  - All sham or saline macaques developed severe interstitial pneumonia
    - All had high levels of detectable virus

Gao Q, Bao L, Mao H, et al. https://science.sciencemag.org/content/early/2020/05/06/science.abc1932

# When will a vaccine be available?

- Phase 2 trials
  - Moderna mRNA vaccine.  Plans to start phase 3 trials in July.
  - Sinovac inactivated virus vaccine.
- Phase 1 trials
  - Cansino viral vector vaccine
  - Invovio DNA vaccine
  - University of Oxford viral vector vaccine
  - BioNTech mRNA vaccine
  - Noravax viral vector vaccine

https://www.statnews.com/feature/coronavirus/drugs-vaccines-tracker

# Final Thoughts

- We are a long way from having a vaccine ready for widespread use in humans.
- We are still discovering which immune responses cause protection and which may cause harm.
- However there is good reason to be optimistic that we will develop effective vaccines.
- It is likely that most vaccines will require multiple doses to develop immunity and the booster doses will be needed periodically.