COVID-19 Vaccine Development—Where are we now?

John Koeppe, MD
June 24, 2020
Disclosures

- None
Learning Objectives

➧ 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

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


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

Immune Responses SARS-CoV-2

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

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

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

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

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

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

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.
  
  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.
  
## Vaccine Disease Enhancement

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

### Table 1

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

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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.

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

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.