COVID-19 Vaccine Development—Where are we now?
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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

Immune responses to Coronaviruses
- 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


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

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


Vector Based Vaccines

- One licensed vaccine: Ervebo (Ebola virus vaccine)
- Uses a replication deficient virus (i.e. adenovirus) to carry the antigen(s) 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

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

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-lasting immunity (and can promote herd immunity)
- Status
  - 3 in development

Concerns

- Studies with MERS and SARS-CoV-1 vaccine in animal models showed "disease enhancement" with exposure to the virus after vaccination.
  - Agner et al. (2016)
  - Lambert et al. (2020)
- Prior RSV vaccination in infants led to higher rates of pneumonia and hospitalization due to an over-exuberant immune response.
  - Kapikian et al. (1969)
  - Kim et al. (1969)

Vaccine Disease Enhancement

De Alwis R, Chen S, Guan X, 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 et al. (2020)

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 et al. (2020)
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
  - Inovio 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.