Coronavirus Overview as it Relates to Vaccine Development

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Vaccines, from concept to implementation

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Conflicts of interest: none

Outline

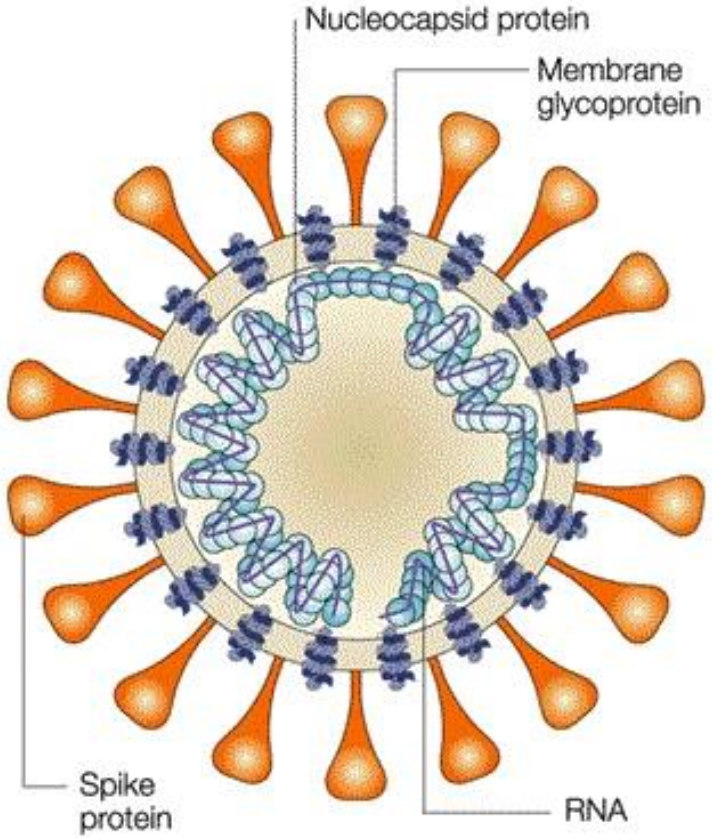
- Coronavirus Virology & Biology
- Transmission
- Pathophysiology
- Clinical features
- Diagnostics
- Immunology

Coronavirus Virology

- >30 known animal CoVs in four genera – A, β, Δ, Γ
- Virus spillover occurs with bats and rodents likely sources of human CoVs
- Seven CoVs known infect humans
  - HCoV-229E, and HCoV-NL63 (alphaCoVs)
  - HCoV-OC43, and HCoV-HKU1 (betaCoVs)
  - SARS-CoV, SARS-CoV-2, and MERS-CoV (betaCoVs)

Coronavirus Virology

- Positive-stranded RNA viruses –prone to mutation
- Genetic drift occurs with SARS-CoV-2 **S, N** and **M** proteins potentially complicating vaccine development



Nature Reviews | Microbiology

https://www.nature.com/articles/nrmicro930/figures/2

Endemic Coronavirus Biology

- Worldwide distribution
- Major cause of common cold-like illness in all ages
- Infection marked seasonal and cyclical patterns
- ~50% of endemic CoV infections are asymptomatic
- Endemic CoVs have a high rate of reinfection; in volunteers it can occur within a year of prior infection

Monto _Coronaviruses Chapter_ Viral Infections of Humans (Kaslow, Stanberry, Le Duc) 2014

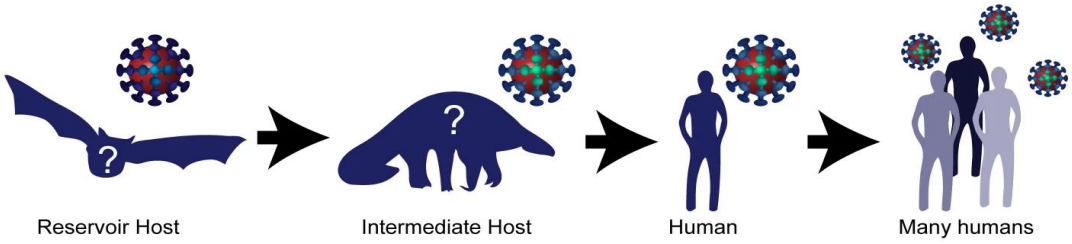
Endemic Coronavirus Biology

- One study, 81.5 % of newly infected individuals had pre-existing virus specific neutralizing antibody
- Uncertain whether pre-existing neutralizing antibody modifies the severity of subsequent re-infections
- Endemic CoV infections involve mainly the surface of the respiratory tract, it is possible that secretory IgA antibody plays a more direct role in protection, as is the case with swine CoV infections

Monto _Coronaviruses Chapter_ Viral Infections of Humans (Kaslow, Stanberry, Le Duc) 2014

SARS-CoV-2 Transmission

- Primarily human to human
- Respiratory – aerosol/droplets/contact - portal of entry: eyes/nose
  - Medical students touch their eyes, nose and or mouth an average of 10 times an hour
- Oral-fecal?
- No recognized mother to fetus transmission



Kwok YLA, et.al., Face touching_ A frequent habit that has implications, Am J Infect Control 43_112-4, 2015
Image source: http://sitn.hms.harvard.edu/flash/2020/covid-19-emerging-viral-diseases-journey-animals-humans/

COVID-19 Transmission Dynamics

- Research suggests that seasonality is likely to play only a minor role in the epidemiology of COVID-19
- **Infections can be symptomatic or asymptomatic**
- Public health interventions strongly associated with reduced epidemic growth:
  - *Masks*
  - *restrictions of mass gatherings*
  - *measures of social distancing*

Juni P, et al, Impact of climate and public health interventions on the COVID-19 pandemic: a prospective cohort, CMAJ 2020. doi: 10.1503/cmaj.200920; early-released May 8, 2020.
Image source: http://cecilcountyhealth.org/wp-content/uploads/2020/05/cartoon-female-and-male-social-distancing-vector.jpg

COVID-19 Pathophysiology(?)

- Virus binds to ACE2 receptors on oral, nasal and ocular mucosal epithelial cells initiating infection
- Infection extends to lungs leading to pneumonia
- Viremia may develop in some patients with dissemination and injury of visceral organs, i.e., heart, renal, gastrointestinal tract (with fecal shedding)
- In some, infection triggers immune dysregulation and immunopathological (autoimmune) responses

Emerging Microbes & Infections, 9:1, 727-732, 2020; Ann Intern Med. 2020 May 6. doi: 10.7326/M20-2003; Nature Medicine 26:502-5, 2020.

COVID-19 Clinical Features Important in Vaccine Development?

- Hypoxia
- Pneumonia
- Organ failure (heart, kidney, multi-organ)
- Hepatitis
- Shock
- Stroke
- Venous thromboembolism
- Pediatric Multi-System Inflammatory Syndrome

CDC COVID-19 Case Definition

Symptomatic COVID-19 Infection

Two or more: fever, chills, rigors, myalgia, headache, sore throat, new olfactory and taste disorder(s)

OR

At least one: cough, shortness of breath, or difficulty breathing

OR

Severe respiratory illness with at least one:

- Clinical or radiographic evidence of pneumonia
- Acute respiratory distress syndrome (ARDS)

AND

Positive SARS-CoV-2 Nucleic Acid Amplification Test (NAAT)

Pfizer *Primary* Efficacy Endpoint Case Definition of *Symptomatic* COVID-19 Infection

Positive SARS-CoV-2 Nucleic Acid Amplification Test (NAAT).

AND at least one of the following:

Fever	Chills
Vomiting	Diarrhea
Sore throat	New loss of taste or smell
New or increased cough	New or increased muscle pain
New or increased shortness of breath	

Pfizer *Secondary* Efficacy Endpoint Case Definition of *Symptomatic* COVID-19 Infection

Positive SARS-CoV-2 Nucleic Acid Amplification Test (NAAT).

AND at least one of the following:

Fatigue	Headache
Nasal congestion or runny nose	Nausea

Included the following additional symptoms defined by CDC (listed at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html)

Pfizer *Secondary* Efficacy Endpoint Case Definition of *Severe Symptomatic* COVID-19 Infection

Positive SARS-CoV-2 Nucleic Acid Amplification Test (NAAT)

AND

- Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO2 ≤93% on room air at sea level, or PaO2/FiO2 <300 mm Hg); or
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO); or
- Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors); or
- Significant acute renal, hepatic, or neurologic dysfunction; or
- Admission to an ICU; or
- Death

SARS-CoV-2 Diagnostics

- Acute infection
  - Virus culture
  - Viral nucleic acid (RNA) detection
  - Antigen detection
- Serologic assays
  - ELISA
  - Lateral-flow
  - Virus neutralization
  - Pseudovirus neutralization

SARS-CoV-2 Immunology

- Antibody seroconversion– IgM appears day 8-12 and is gone by week 13. IgG appears around day 14
  - Serum contains neutralizing antibody; convalescent plasma appears to have some therapeutic benefit
- Both CD4+ and CD8+ T cells are detected about 7 days after onset of symptoms
  - SARS- CoV-1 mouse studies showed that induction or passive transfer of virus- specific CD4+ and CD8+ T cells increased survival. Other studies found that some vaccines could induce detrimental T cell responses

Tay MZ, et. al, The trinity of COVID-19- immunity, Inflammation and Infection. Nature Reviews Immunology, April 2020

SARS-CoV-2 Unknowns

- What proportion of the population need to become infected and/or immunized to afford to community immunity (herd immunity)?
  - Depends on the efficacy of the vaccine.
  - https://www.sciencedirect.com/science/article/pii/S0140673620323187?via%3Dihub
- Will COVID-19 infection provide broad, long-term protection against SARS-CoV-2 reinfection?
  - https://www.cancer.gov/news-events/cancer-currents-blog/2020/coronavirus-antibodies-protect-against-future-infection
- Will annual COVID-19 booster vaccines be needed?
- Will SARS-CoV-2 mutations impact vaccine effectiveness?

References

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THANK YOU