COVID Update

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Disclosures

Dr. Zwickey is supported by NCCIH Grant 2 R90AT008924-01.

Dr. Zwickey is supported as Professor of Immunology and Chair of the Department of Health Science at the National University of Natural Medicine.

Dr. Zwickey is co-owner of the company ZamiaLife and advisor to Flora Medicine but will not be speaking of their products during this presentation.

Dr. Zwickey is on the Scientific Advisory Board for Burt's Bees but won't be speaking about Burt's Bees products during this presentation.

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Overview

- Immune response to COVID
- Therapies for COVID
- Vaccine development

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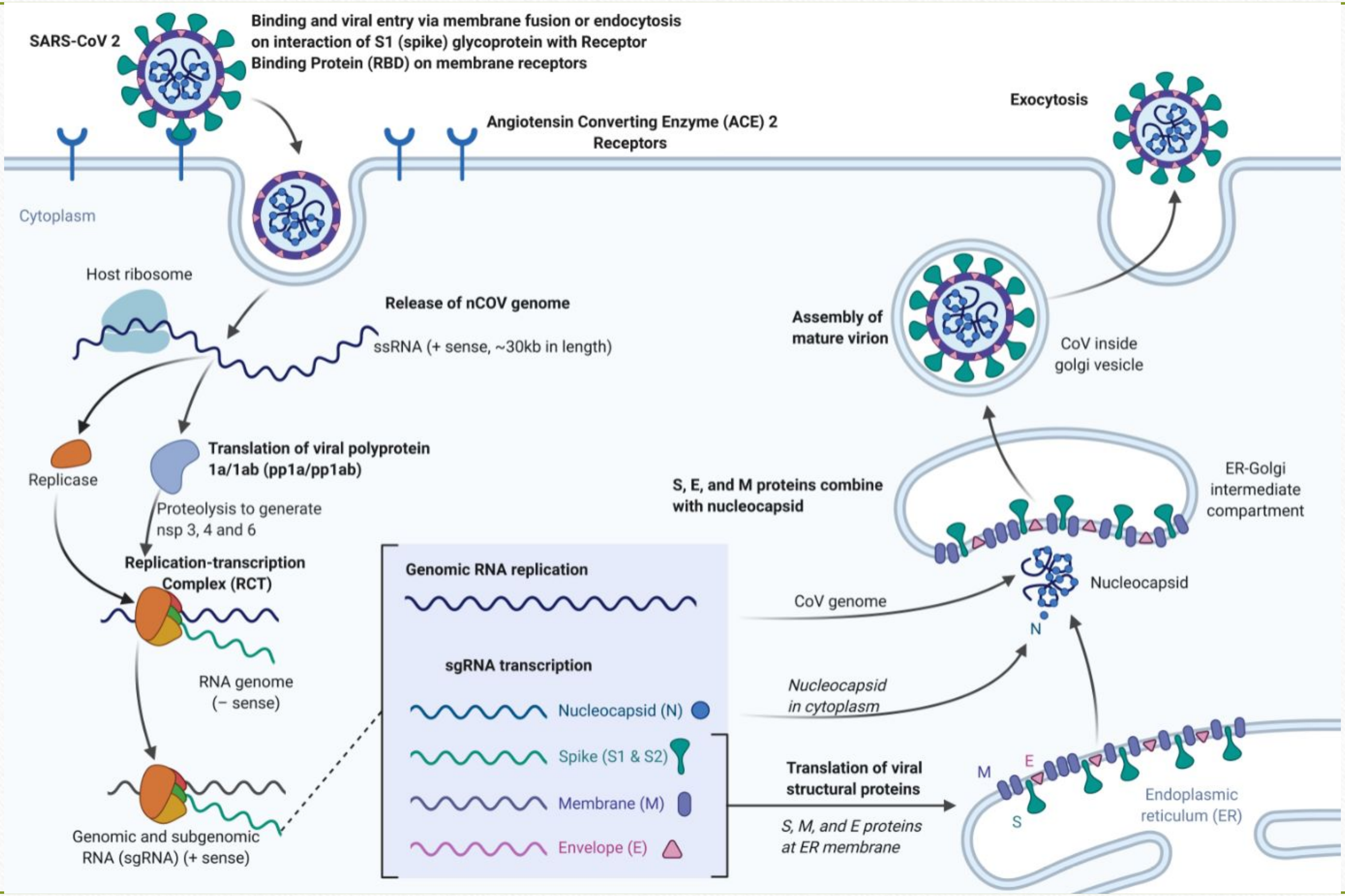

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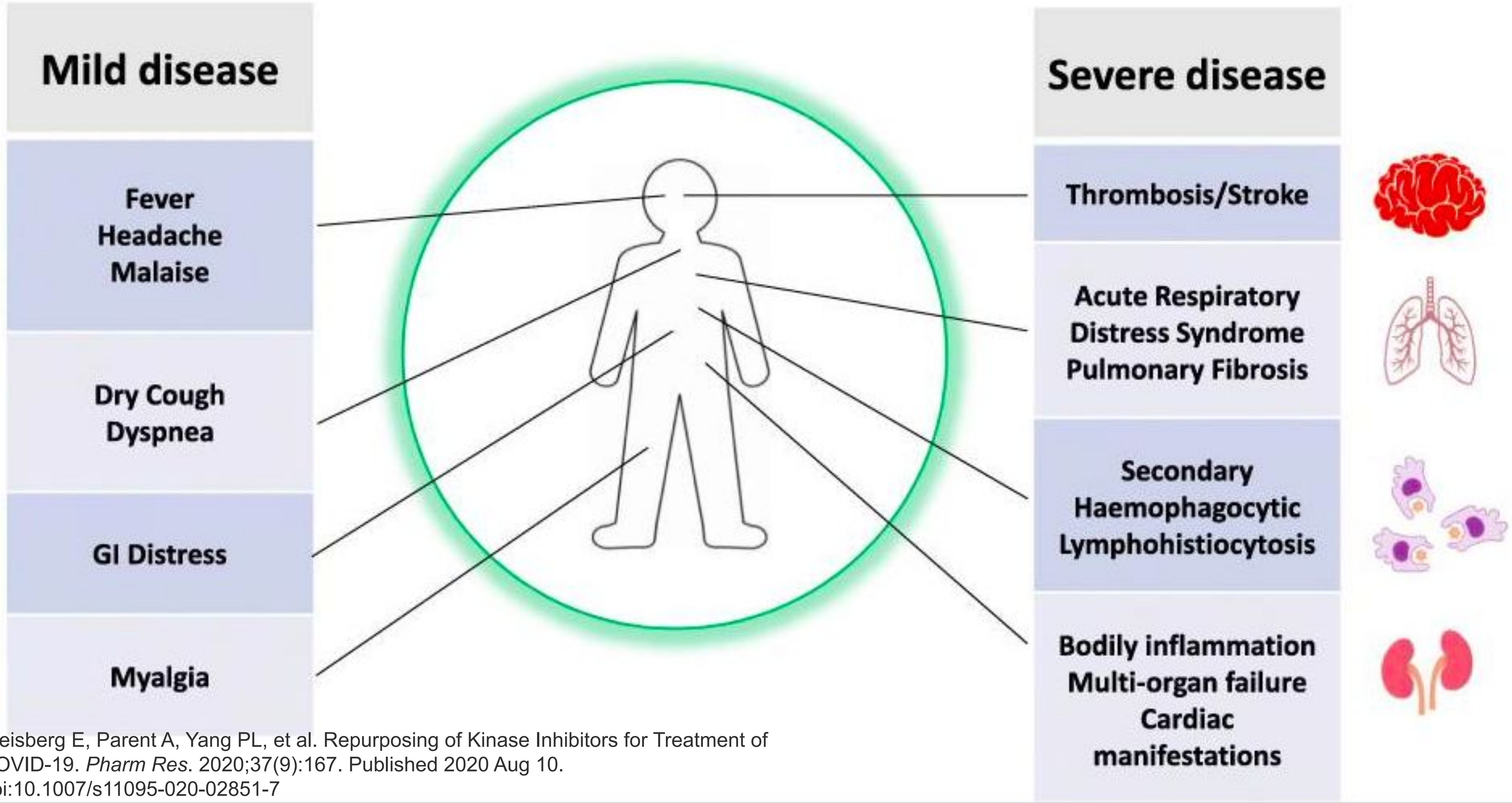
COVID-19 Symptoms



Weisberg E, Parent A, Yang PL, et al. Repurposing of Kinase Inhibitors for Treatment of COVID-19. *Pharm Res*. 2020;37(9):167. Published 2020 Aug 10. doi:10.1007/s11095-020-02851-7

Immune Response Overview

Inflammation → Innate Immunity → Specific Immunity → Resolution → Memory

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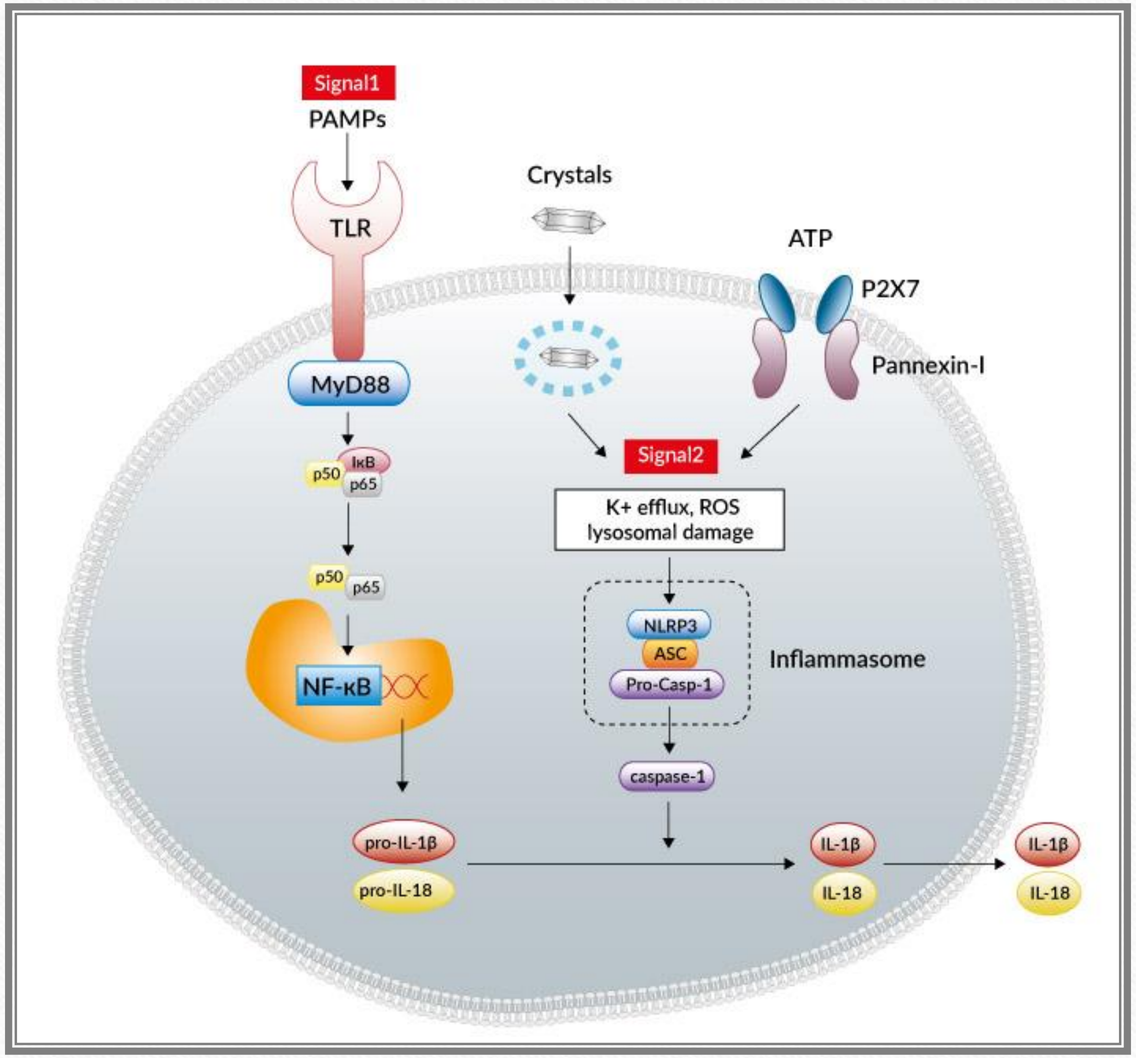
Cytokines associated with Immunity

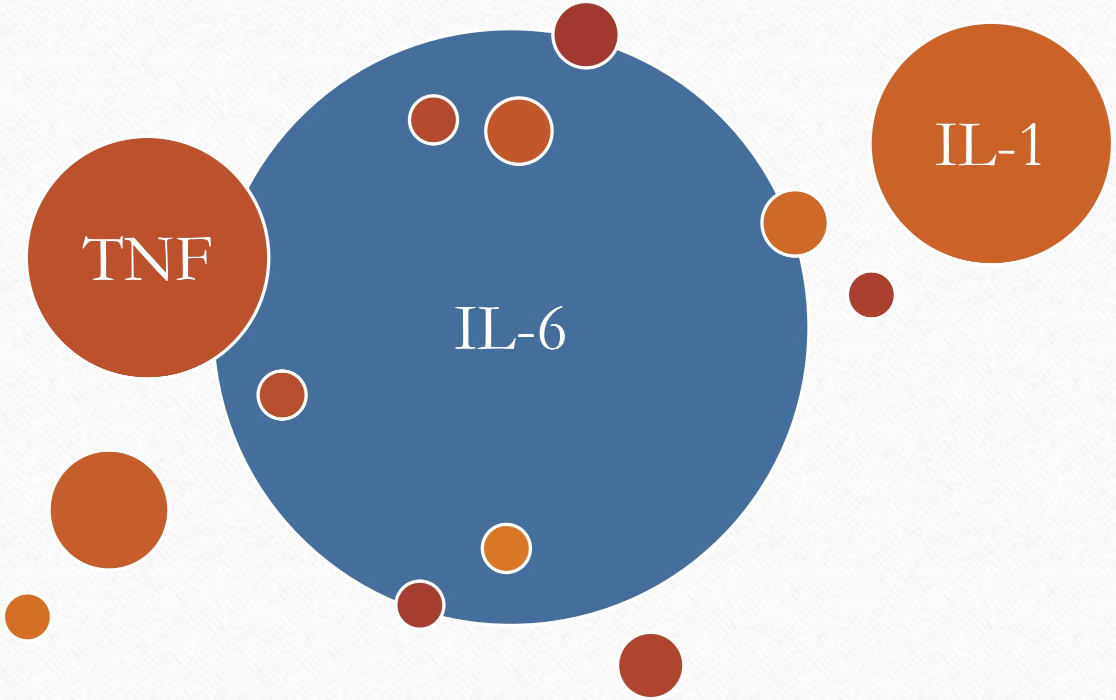
Inflammation	Innate Immunity	Specific Immunity	Resolution	Memory
IL-1 beta IL-6 TNF-alpha	IL-12 IL-4 IL-10 IL-23	IFN-gamma IL-4, IL-5, IL-13 IL-17, IL-22	TGF-beta IL-10	

NLRP3 Inflammasome

- https://www.invivogen.com/review-nlrp3-inflammasome



Pathogenesis of COVID - Pneumonia



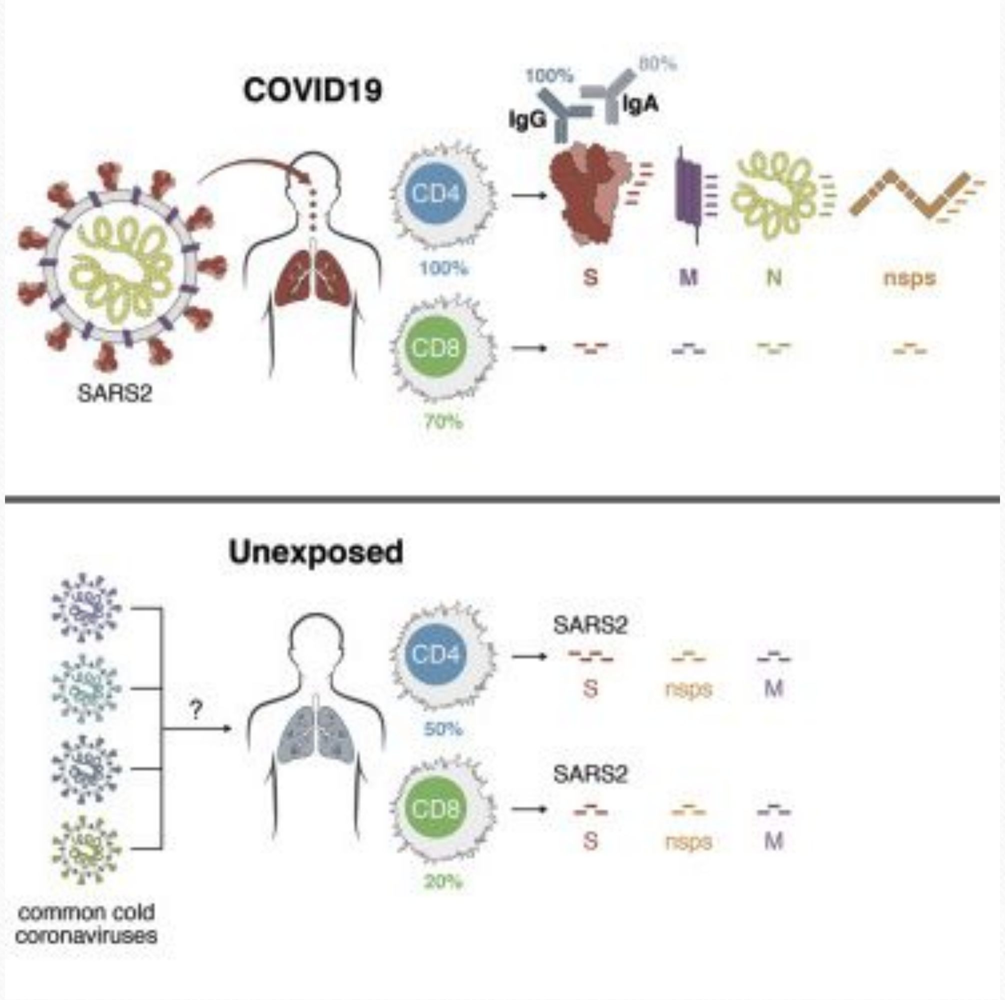
Immune Response to COVID

COVID

- 100% CD4 T cell response to COVID.
- 100% generate antibodies.
- 70% generate CD8 T cells.

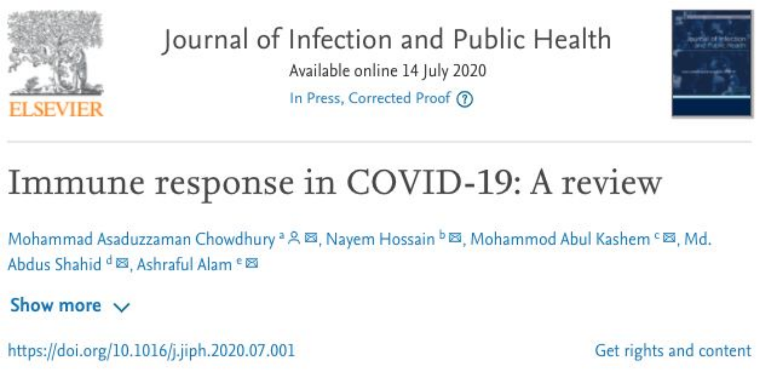
Coronavirus

- 50% mount CD4 responses
- 20% mount CD8 responses
- No antibodies



https://doi.org/10.1016/j.cell.2020.05.015

Immune Response to COVID



Journal of Infection and Public Health
Available online 14 July 2020
In Press, Corrected Proof

Immune response in COVID-19: A review

Mohammad Asaduzzaman Chowdhury [a], Nayem Hossain [b], Mohammod Abul Kashem [c], Md. Abdus Shahid [d], Ashraful Alam [e]

Show more

https://doi.org/10.1016/j.jiph.2020.07.001

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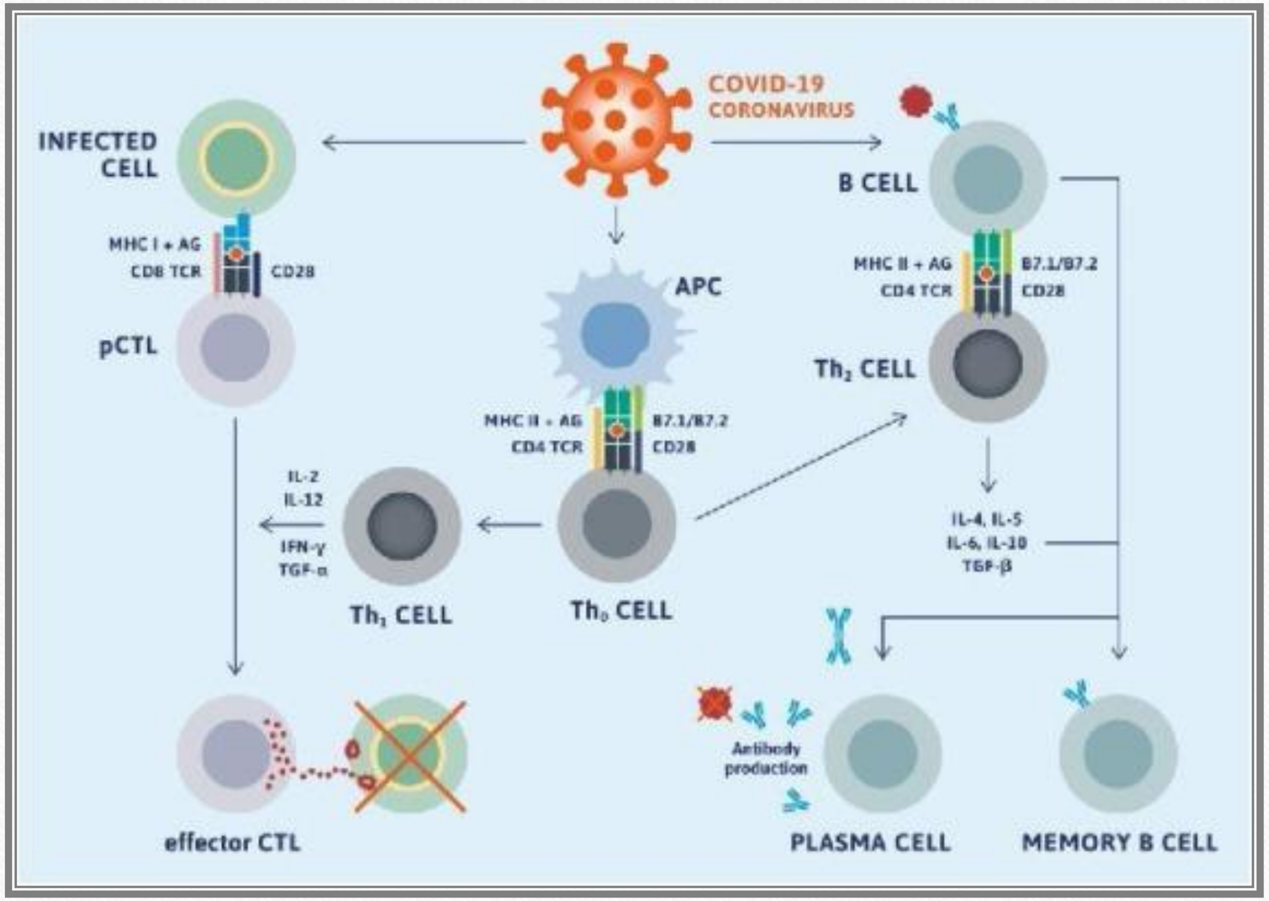
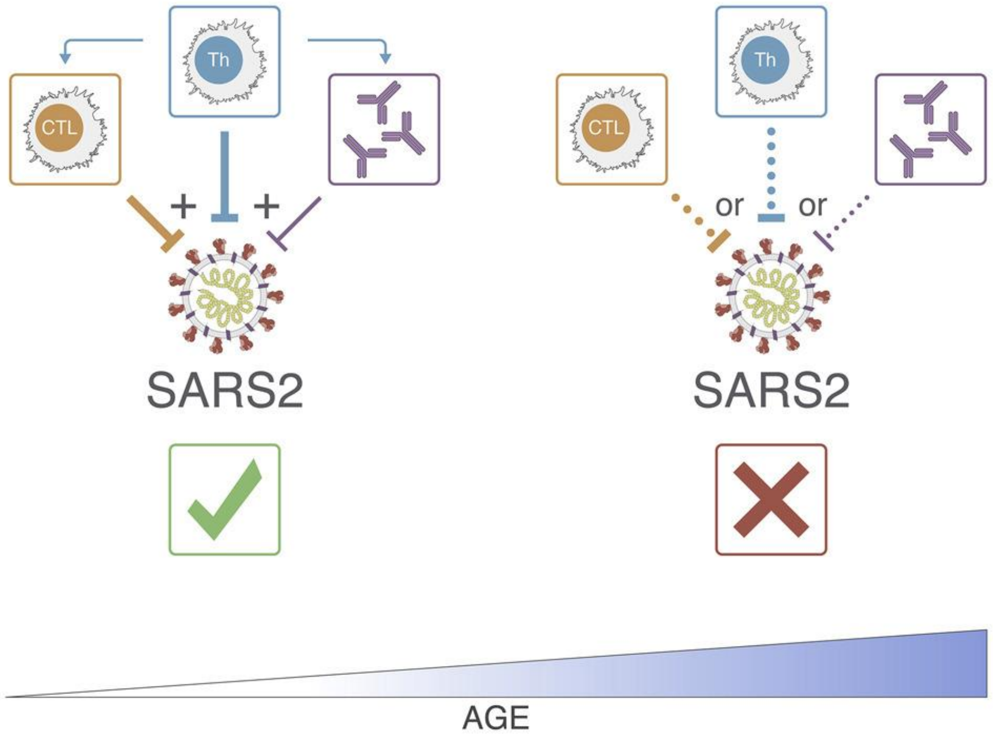


# of neutralizing antibodies don't correlate with disease severity

Patients with greatest disease severity have low levels of CD8 and CD4 T cells



Cell DOI: (10.1016/j.cell.2020.09.038)

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Immune Response to COVID

Stuck here
IL-6

Don’t have enough naïve CD4 and CD8 cells

Don’t make it here

?

Different Responses

- Age
- Gender
- Race/Ethnic
- Hyper-nutrition
- Inflammatory Disease
- Smoking

Age and COVID

Immunosenescence

- Specific immunity decreases with age

Malnutrition

- All viral disease increases with age; lower vitamin and micronutrient levels

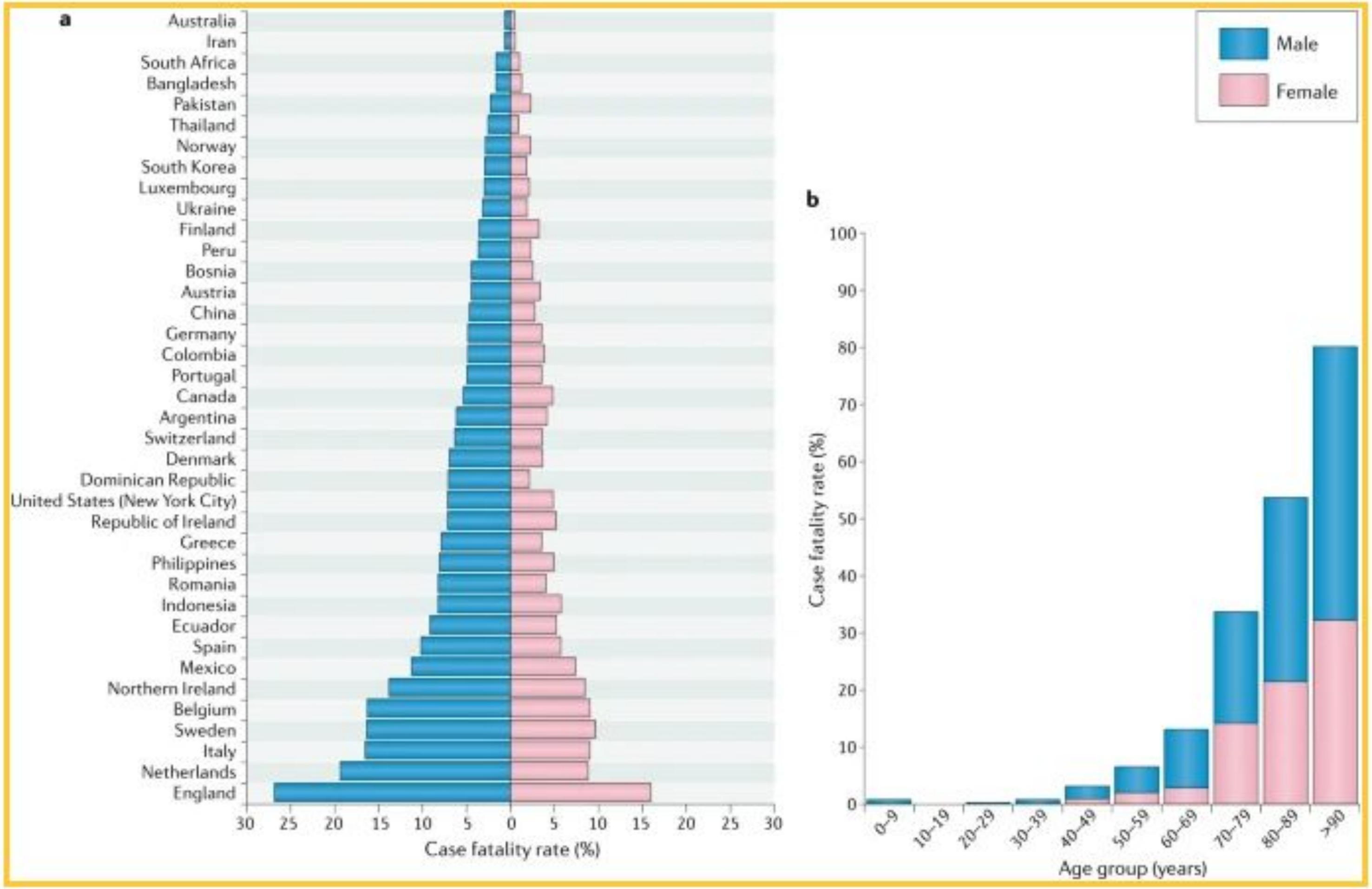
Inflammatory diseases

- Often already have inflammation

Gender and COVID

Scully, E.P., Haverfield, J., Ursin, R.L. *et al.* Considering how biological sex impacts immune responses and COVID-19 outcomes. *Nat Rev Immunol* **20,** 442–447 (2020). https://doi.org/10.1038/s41577-020-0348-8

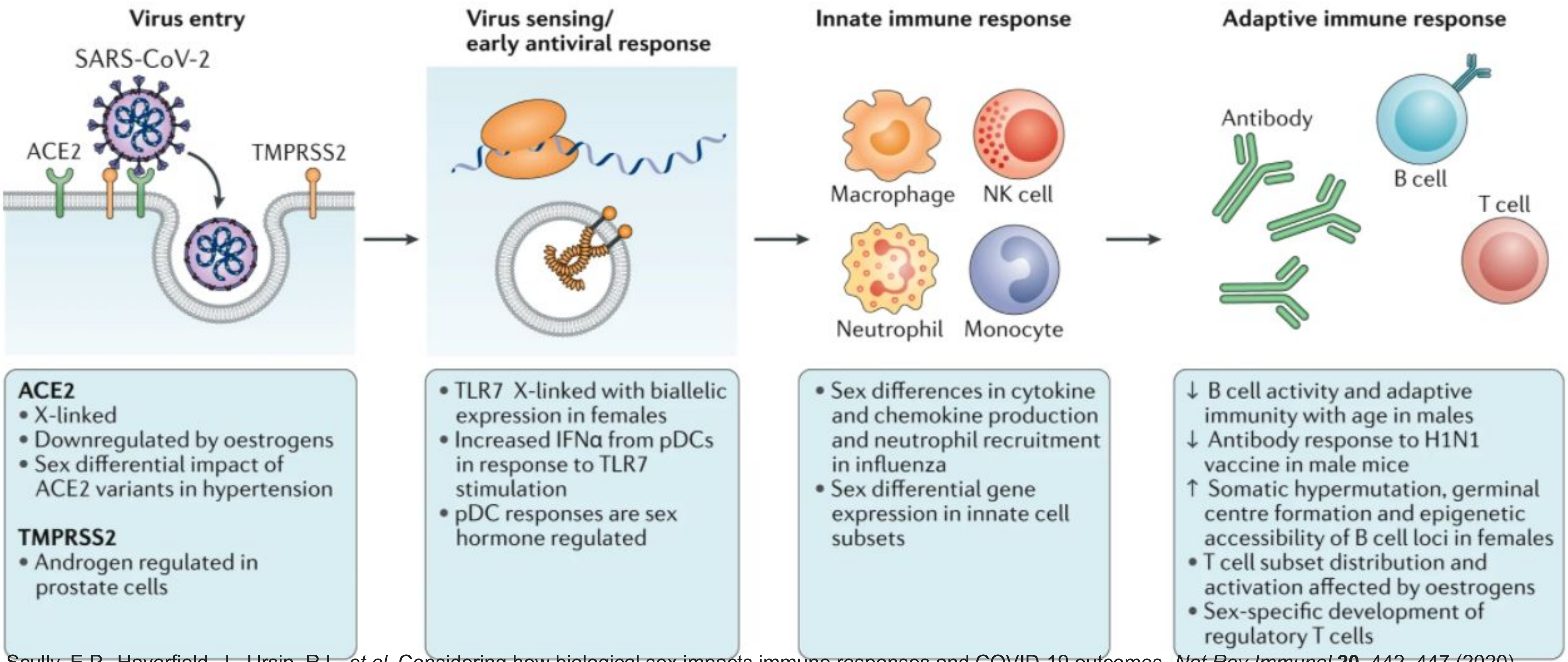
Fig. 1: Comparative analyses of COVID-19 case fatality rates by country, sex and age.



a | COVID-19 case fatality rates (CFRs) for males and females across 38 countries or regions reporting sex-disaggregated data on COVID-19 cases and deaths. CFR was calculated as the total number of deaths divided by the total number of cases for each sex multiplied by 100. The male CFR is higher than the female CFR in 37 of the 38 regions, with an average male CFR 1.7 times greater than the average female CFR ($P < 0.0001$, Wilcoxon signed rank test). **b** | Average COVID-19 CFRs for males and females stratified by age. The data represent 12 countries currently reporting sex- and

Fig. 2: Known sex differences that may impact immune responses to SARS-CoV-2 and COVID-19 progression.

From: Considering how biological sex impacts immune responses and COVID-19 outcomes



Scully, E.P., Haverfield, J., Ursin, R.L. *et al.* Considering how biological sex impacts immune responses and COVID-19 outcomes. *Nat Rev Immunol* **20,** 442–447 (2020). https://doi.org/10.1038/s41577-020-0348-8

Gender and COVID

TLRs

- Women have more TLR3, 7, and 9 – viral infections
- Men have more TLR2 and 4 – bacterial infections

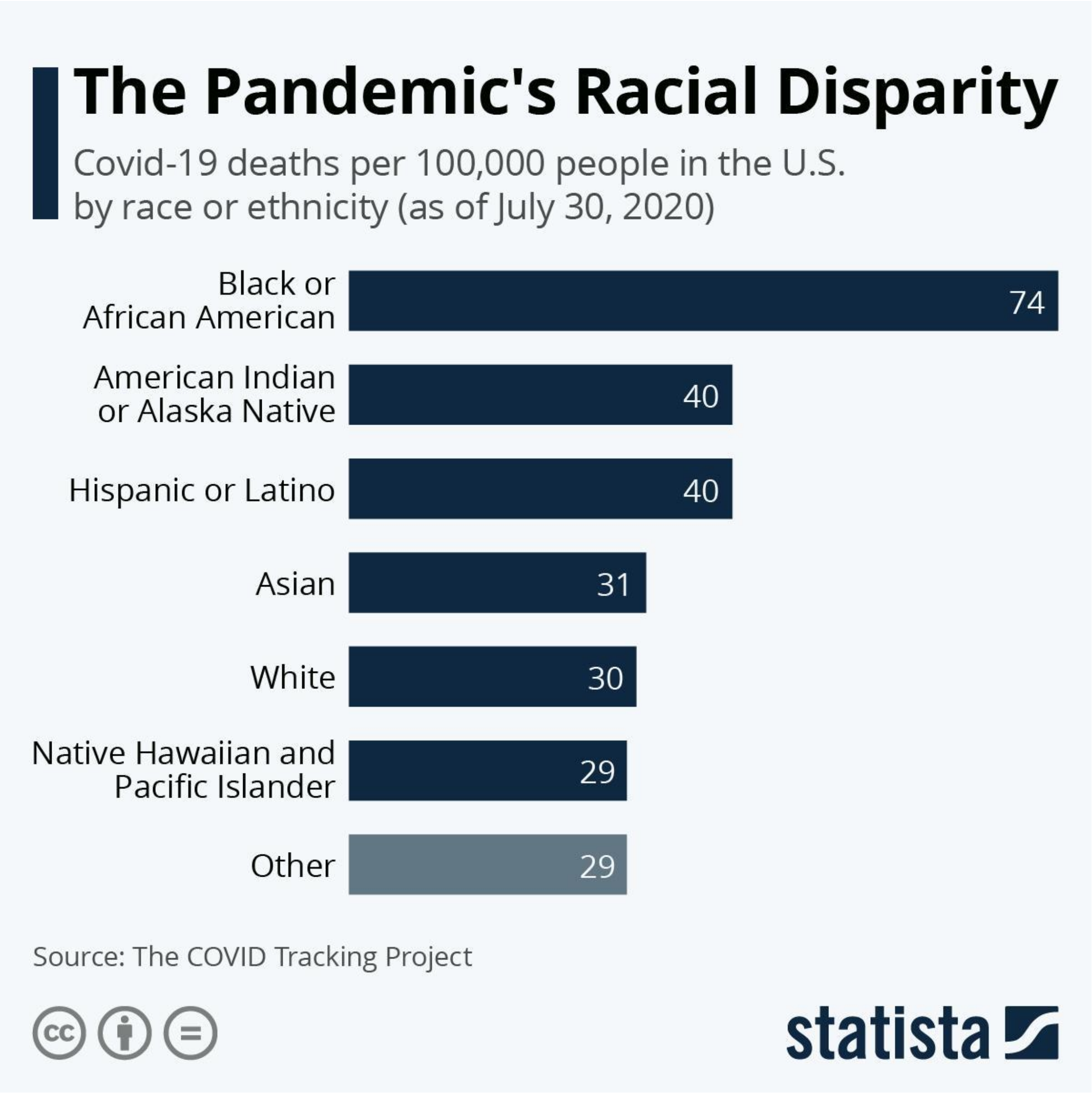
Hormones

- Estrogen drives higher Th1 response

Melatonin

- Women have more   anti-oxidant; Decreases the NLRP3 inflammasome

Race/Ethnicity and COVID



Race/Ethnicity and COVID

Discrimination

- Access to health care, housing, education, safe criminal justice and finance increased stress inflammation

Healthcare Access and Utilization

- Less likely to be insured, have transportation, ability to take time off
- Communication and language differences; Racial and cultural differences between patients and providers; Distrust of medical system

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Race/Ethnicity and COVID

Occupation

- Disproportionately represented in essential work settings increased exposure

Pre-existing Medical Conditions

- COPD, Obesity, Heart conditions, Type II diabetes, Sickle cell disease
- Smoking

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Nutrition and COVID

Malnutrition

- Insufficient protein intake
  - Impairs immune activation
  - Longer viral persistence
  - Increased trafficking of inflammatory cells to the lungs

Adiposity

- Sarcopenic obesity
  - Obese with low muscle mass
  - Systemic low grade inflammation
  - Poor effector function in T cells (low cytokine secretion, lower killing)

https://doi.org/10.3389/fmed.2020.00146

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Nutrition and COVID: Micronutrients

Vitamins A & D

- Antibody function
- T cell proliferation
- Treg production

Other vitamins

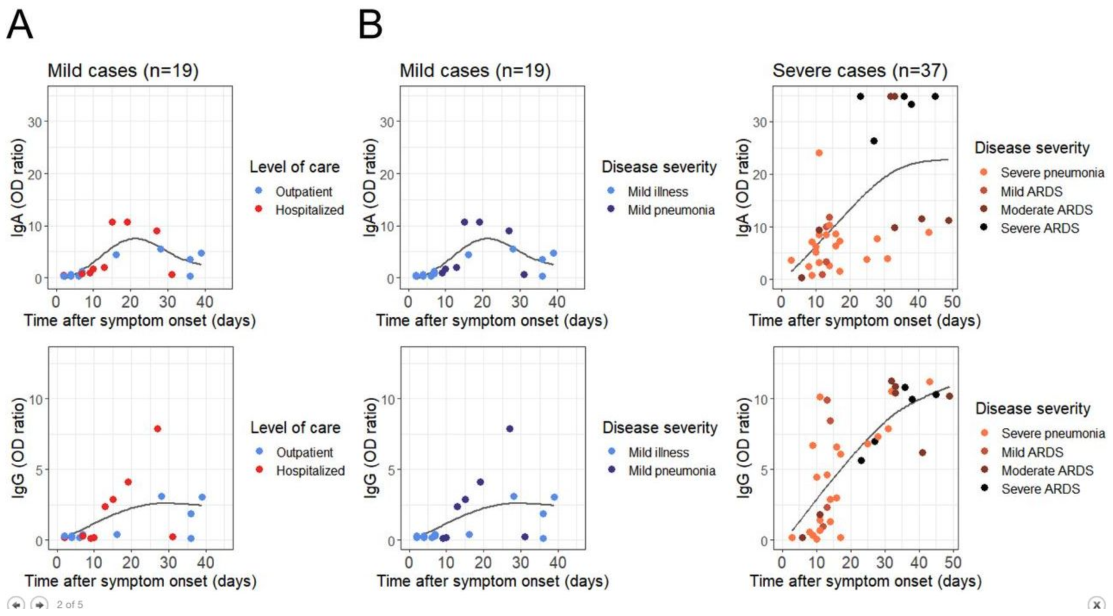
- Vitamins B, C, E
- Selenium
- Zinc

https://doi.org/10.3389/fmed.2020.00146

Table 1. Certain micronutrients have key roles in the immune system [2,7–9].

Immune Function Roles	Micronutrient	Comments
Physical and biochemical barriers		
Maintenance of structural and functional integrity of mucosal cells in innate barriers (e.g., skin, respiratory tract)	Vitamin A	Normal differentiation of epithelial tissue; retinoic acid essential to imprint T and B cells with gut-homing specificity and array T cells and IgA+ cells into intestinal tissues [8]. important for intestinal immune response, thus supporting the gut barrier [10–12]; carotenoids (either provitamin A or nonprovitamin A carotenoids) have immunoregulatory actions including reducing the toxic effects of ROS and regulating membrane fluidity and gap-junctional communication [13]
	Vitamin D	Calcitriol regulates antimicrobial proteins (cathelicidin and β-defensin), responsible for modifying intestinal microbiota to a healthier composition and supporting the gut barrier [10,14], as well as protecting the lungs against infection [15]; increases tight junction protein expression, E-cadherin, and connexion 43 in the gut [16–18]; maintains renal epithelial barrier function [19]; enhances corneal epithelial barrier function [20]
	Vitamin C	Promotes collagen synthesis and protects cell membranes from damage caused by free radicals, thus supporting integrity of epithelial barriers [8]; enhances keratinocyte differentiation and lipid synthesis as well as fibroblast proliferation and migration [21]
	Vitamin E	Protects cell membranes from damage caused by free radicals and support the integrity of epithelial barriers [7,8]
	Vitamins B6, B12 and folate	All involved in intestinal immune regulation (e.g., by mediating lymphocyte migration into the intestine in the case of vitamin B6, while folate is essential for the survival of regulatory T cells in the small intestine, and human gut microbes use vitamin B12 as a cofactor for metabolic pathways), thus supporting the gut barrier [10,22]
	Iron	Essential for differentiation and growth of epithelial tissue [3]
	Zinc	Helps maintain integrity of skin and mucosal membrane (e.g., cofactor for metalloenzymes required for cell membrane repair [23])

Gombart AF, Pierre A, Maggini S. A Review of Micronutrients and the Immune System-Working in Harmony to Reduce the Risk of Infection. *Nutrients*. 2020;12(1):236. Published 2020 Jan 16. doi:10.3390/nu12010236



Disease Severity and Antibody response

- Systemic and mucosal antibody secretion specific to SARS-CoV-2 during mild versus severe COVID-19
- Carlo Cervia, et al
- bioRxiv 2020.05.21.108308; doi: https://doi.org/10.1101/2020.05.21.108308

Inflammation and COVID

- Evidence of a multi-system inflammatory disease
  - Children & Adults
- 16 patients
- Five were reported as Hispanic, nine as African American, one as Asian, and one as a United Kingdom–born man of African ethnicity.
- Nine patients had no reported underlying medical conditions;
- Six were obese, one had poorly controlled diabetes mellitus type 2 (hemoglobin A1C >9.0%), two had hypertension, and one had obstructive sleep apnea.
- Eight patients had documented respiratory illness before developing symptoms of MIS-A, and eight did not.

Morris SB, Schwartz NG, Patel P, et al. Case Series of Multisystem Inflammatory Syndrome in Adults Associated with SARS-CoV-2 Infection — United Kingdom and United States, March–August 2020. MMWR Morb Mortal Wkly Rep 2020;69:1450–1456. DOI: http://dx.doi.org/10.15585/mmwr.mm6940e1

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Long-term consequences of disease

Heart

- Lasting damage to heart muscle

Brain

- Strokes and seizures

Lungs

- Pneumonia scar tissue

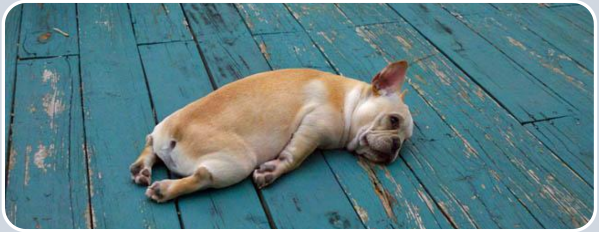
More long-term consequences of disease

Liver and Kidneys

- Micro-clots

Mood

- Depression, anxiety, PTSD



Fatigue

- Long term fatigue syndrome

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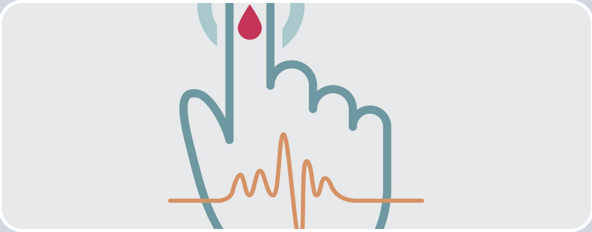
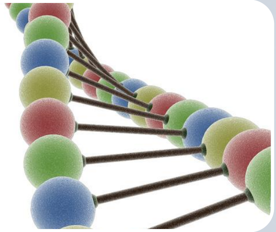
And more long-term consequences of disease





Diabetes?

- ACE2 is on pancreas

Autoimmunity?

- Bystander effect

Epigenetics?

- Next generations?

Treatments

- Oxygen therapy
- Corticosteroids
- Antiviral therapy
- Immunomodulatory drugs

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Oxygen Therapy

- Patient: a SpO2 < 93-94% (< 88-90% if COPD) or a respiratory rate > 28-30 / min, or dyspnoea,
- Administration of oxygen by a 40% Venturi mask
    - After a 5 to 10 minutes reassessment, if the clinical and instrumental picture has improved the patient continues the treatment and undergoes a re-evaluation within 6 hours.

Cascella M, Rajnik M, Cuomo A, et al. Features, Evaluation, and Treatment of Coronavirus (COVID-19) [Updated 2020 Aug 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554776/

Corticosteroids

- Systemic corticosteroids for the treatment of viral pneumonia or acute respiratory distress syndrome (ARDS) are not recommended,
- In severe COVID-ARDS these drugs are usually used (e.g., methylprednisolone 1 mg/Kg/day).
- The RECOVERY trial: Dexamethasone reduces deaths by one-third among critically ill COVID-19 patients.
  - In the intervention group, 2,100 patients received dexamethasone (6 mg/day for 10 days) whereas in the control group patients (n=4,300) received standard care for the disease.

Cascella M, Rajnik M, Cuomo A, et al. Features, Evaluation, and Treatment of Coronavirus (COVID-19) [Updated 2020 Aug 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554776/

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Anti-viral Therapy

- No antiviral treatments have been approved,
- Llopinavir/ritonavir (400/100 mg orally every 12 hours)
  - Randomized, controlled, open-label trial demonstrated no benefit with lopinavir/ritonavir treatment compared to standard care.
  - Remdesivir (GS5734) — an inhibitor of RNA polymerase with in vitro activity against multiple RNA viruses, including Ebola — could be effective for both prophylaxis and therapy of HCoVs infections.
  - tested in a rhesus macaque model
- Flu medication tried include: Oseltamivir, Favipiravir (in vitro), broad-spectrum antiviral, arbidol.

Cascella M, Rajnik M, Cuomo A, et al. Features, Evaluation, and Treatment of Coronavirus (COVID-19) [Updated 2020 Aug 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554776/

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Immunomodulatory Drugs

- Chloroquine (500 mg every 12 hours), and hydroxychloroquine (200 mg every 12 hours)
  - Non-randomized trial showed that hydroxychloroquine was significantly associated with viral load reduction until viral disappearance and this effect was enhanced by the macrolides azithromycin.
  - Chloroquine and hydroxychloroquine may induce the downregulation of the adhesion molecules of the cell surface, reducing the production of proinflammatory cytokines, stimulating phagocytosis by alveolar macrophages, and inhibiting the activation and mobilization of neutrophils.
  - Concomitant use of hydroxychloroquine with azithromycin can lead to a higher risk of QT interval prolongation and cardiac arrhythmias. Chloroquine can also induce QT prolongation.

Cascella M, Rajnik M, Cuomo A, et al. Features, Evaluation, and Treatment of Coronavirus (COVID-19) [Updated 2020 Aug 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554776/

Serotherapy

- Antibodies taken from the blood of healed individuals
  - Dose of antibodies necessary for the treatment of a single patient with SARS-CoV-2, requires antibodies from at least three patients recovered from the SARS-CoV-2 infection.
  - Clinical trial launched (June 11, 2020) for investigating an antibody cocktail for the prevention and treatment of COVID-19.

Cascella M, Rajnik M, Cuomo A, et al. Features, Evaluation, and Treatment of Coronavirus (COVID-19) [Updated 2020 Aug 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554776/

Inflammation Inhibitors - Biologics

- Tocilizumab-humanized IgG1 monoclonal antibody, directed against the IL-6 receptor (Italy)
  - commonly used in the treatment of rheumatoid arthritis, juvenile arthritis, giant cell arthritis, Castleman's syndrome, and for managing toxicity due to immune checkpoint inhibitors.
- Sarilumab- anti-IL-6 receptor antibody; Phase 2/3 RCT is ongoing (United States)
- Anakinra- recombinant IL-1 receptor antagonist; retrospective analysis showed that in patients with moderate-to-severe ARDS, and hyperinflammation (C-reactive protein ≥100 mg/L, ferritin ≥900 ng/mL, or both), the use of anakinra induced clinical improvement in 72% of patients.
- Acalabrutinib - selective Bruton tyrosine kinase inhibitor, which regulates macrophage signaling and activation; tested on 19 patients with severe COVID-19 in a prospective off-label clinical study; treatment improved oxygenation in a majority of patients, ameliorating measures of inflammation such as C-reactive protein and IL-6.

Cascella M, Rajnik M, Cuomo A, et al. Features, Evaluation, and Treatment of Coronavirus (COVID-19) [Updated 2020 Aug 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554776/

Anti-coagulants

- Patients have a higher incidence of venous thromboembolism and anticoagulant therapy is associated with reduced ICU mortality,
- Thromboprophylaxis.
- For thrombophilia or thrombosis, full therapeutic-intensity anticoagulation (e.g., enoxaparin 1 mg/kg twice daily) is indicated.

Cascella M, Rajnik M, Cuomo A, et al. Features, Evaluation, and Treatment of Coronavirus (COVID-19) [Updated 2020 Aug 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554776/

Potential Medications

Weisberg E, Parent A, Yang PL, et al. Repurposing of Kinase Inhibitors for Treatment of COVID-19. *Pharm Res*. 2020;37(9):167. Published 2020 Aug 10. doi:10.1007/s11095-020-02851-7

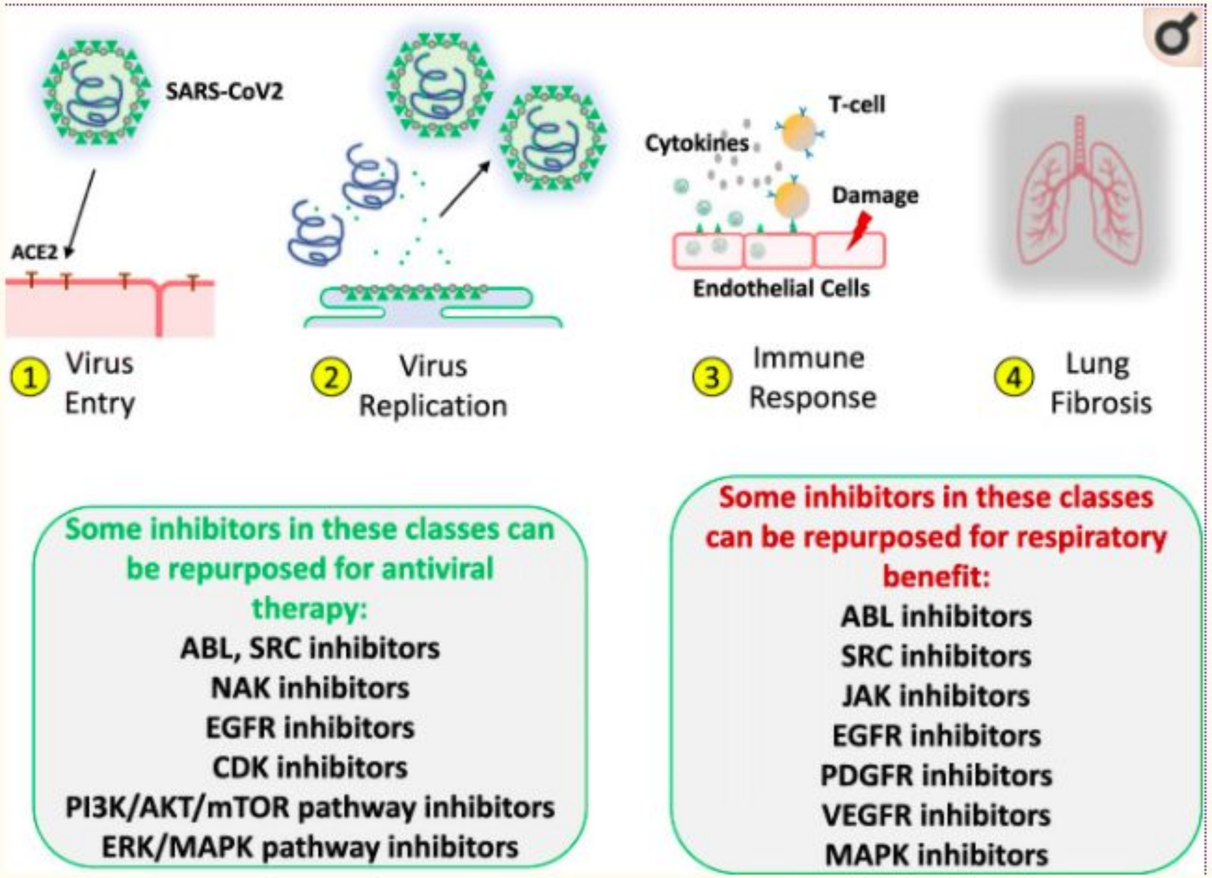


Figure 3.

Repurposing of kinase inhibitors as antiviral therapies and for respiratory benefit.

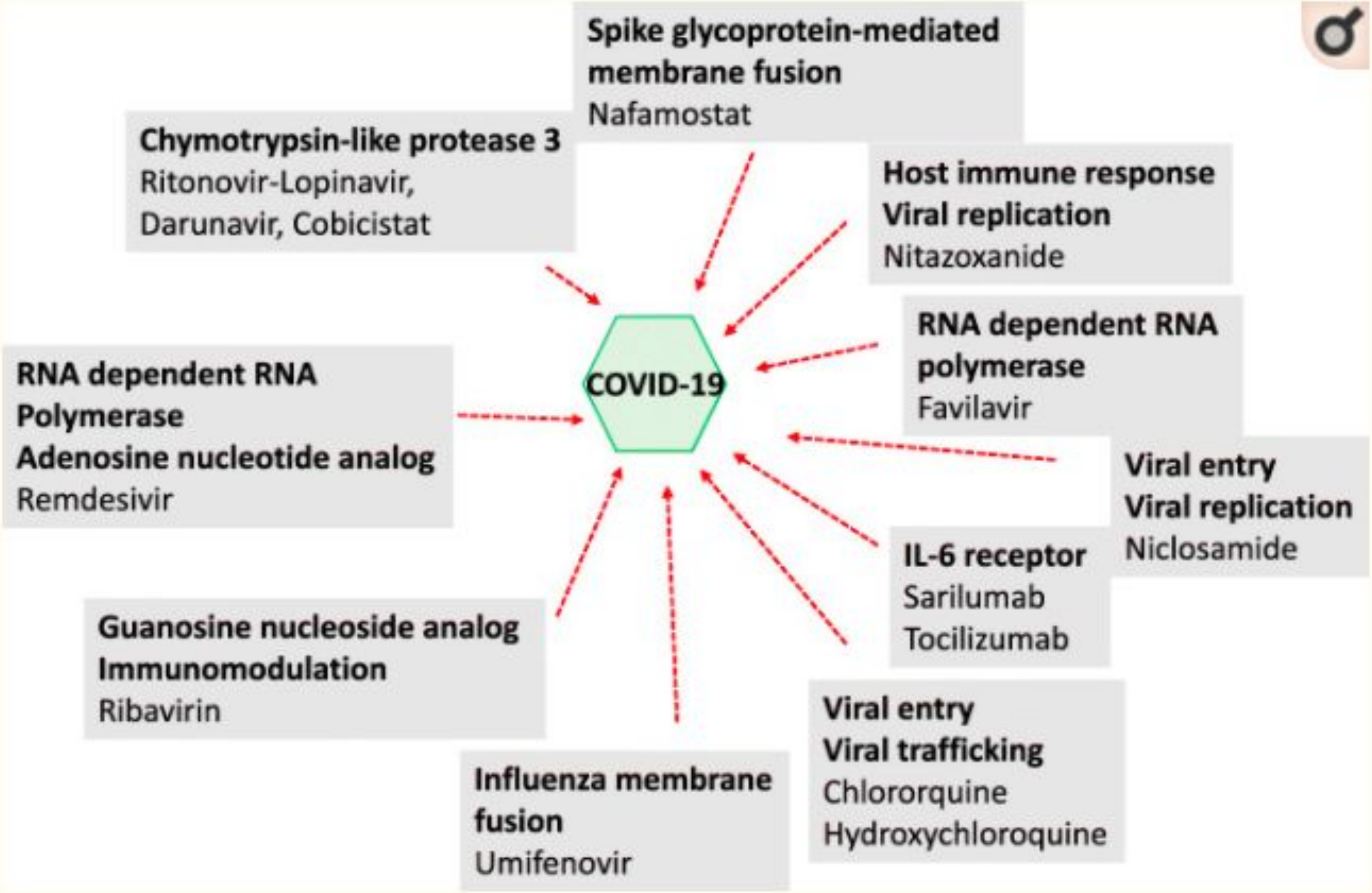


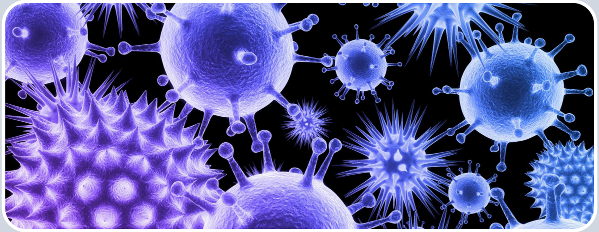
Figure 4.

Drug therapies under investigation for COVID-19.

Natural Therapies

- Prevention and/or treatment
- No research on any of these therapies for COVID specifically

Strategy



Kill virus directly

Block virus life-span

Stimulate anti-viral immunity

Anti-viral herbs

Mint family

- Peppermint, spearmint, lemon balm, self-heal, sage, oregano
- Tea, tincture, dried herb in capsules, essential oils

Fennel

- Tea, infusion, dried herb

Block life-span of virus

- Herbs can
  - block uptake of virus
  - block RNA DNA reverse transcriptase
  - block cellular processes required for replication

Elderberry

- Disrupts lipid rafts so viruses can't enter cells

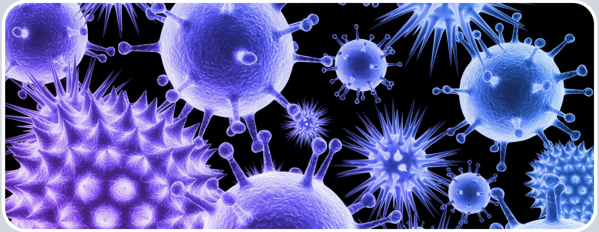
Calendula

- Blocks reverse transcriptase

Hyssopus officinalis (mint family)

- Blocks viral replication

Strategy



Kill virus directly

Block virus life-span

Stimulate anti-viral immunity

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How do we stimulate ‘anti-viral’ immunity?

Stimulate an anti-viral immune response

Resolve infection and inflammation

Reduce the ‘cytokine storm’

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Stimulate Anti-viral Immunity

Astragalus

Elderberry

Berberine (Goldenseal, Oregon Grape)

Echinacea

Lemon Balm

Oregano

Mushrooms

- Reishi
- Maitake
- Cordyceps

Resolution

In order to fully resolve an infection, you need to make 'resolvins.'

You must have omega 3s in your diet to make resolvins.

Omega 3/Omega 6 ratio should be 1:1, but is currently 1:10 or 1:20!

We need more sources of omega 3s in our diet!

Natural ways to decrease IL-6

Feverfew

Lemon Balm

Ashwagandha

Microbiota and COVID-19

Zuo et al. 2020

Shotgun metagenomic sequencing analyses of fecal samples from 15 patients with COVID-19

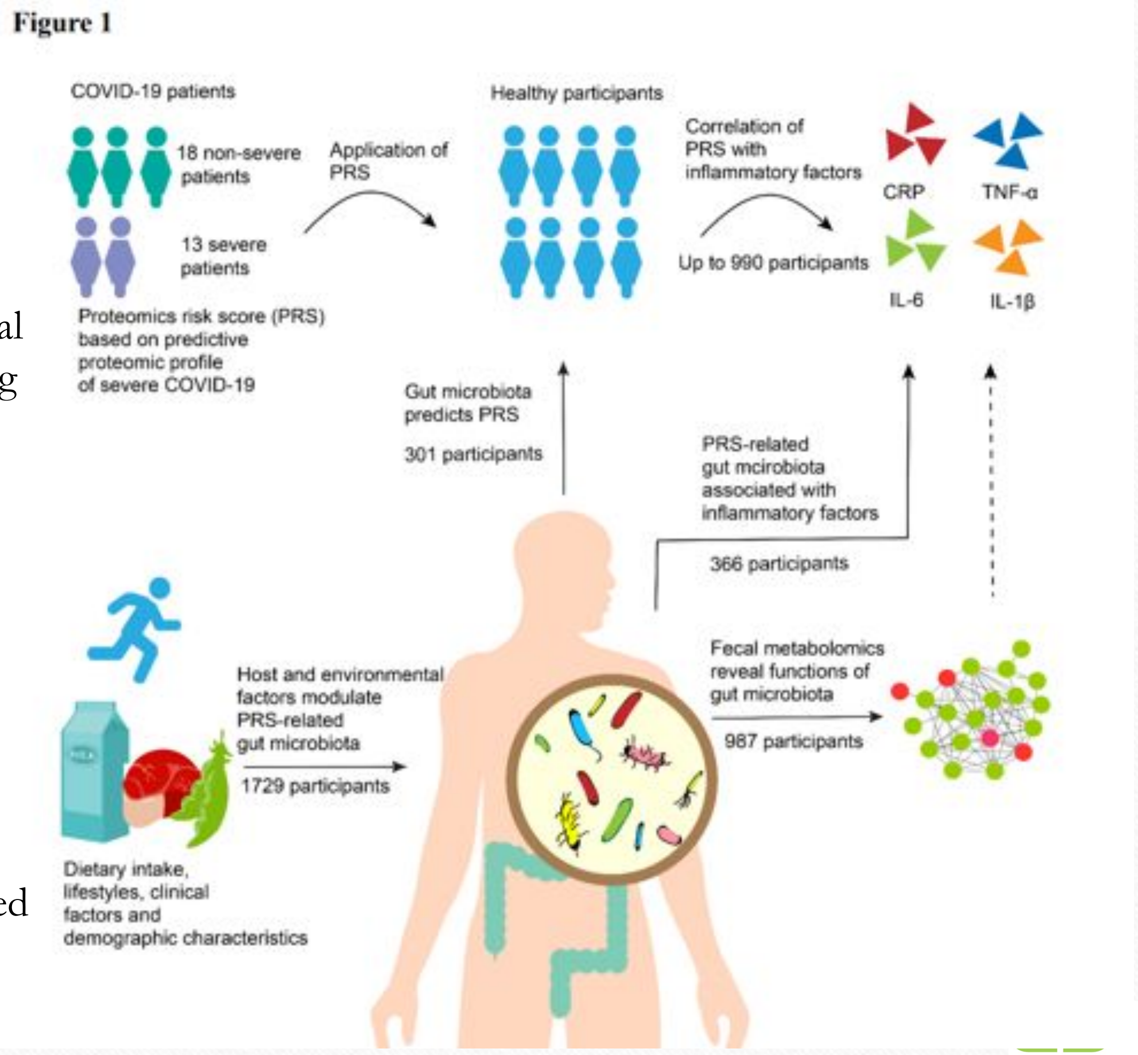
Patients with COVID-19 had significant alterations in fecal microbiomes compared with controls, characterized by enrichment of opportunistic pathogens and depletion of beneficial commensals, at time of hospitalization and at all timepoints during hospitalization.

Gou et al. Pre-Print 2020

Proteomic risk score based on 20 blood proteomic biomarkers which predict the progression to severe COVID

Proteomics data from 31 COVID-19 patients vs 2413 Chinese participants without infection

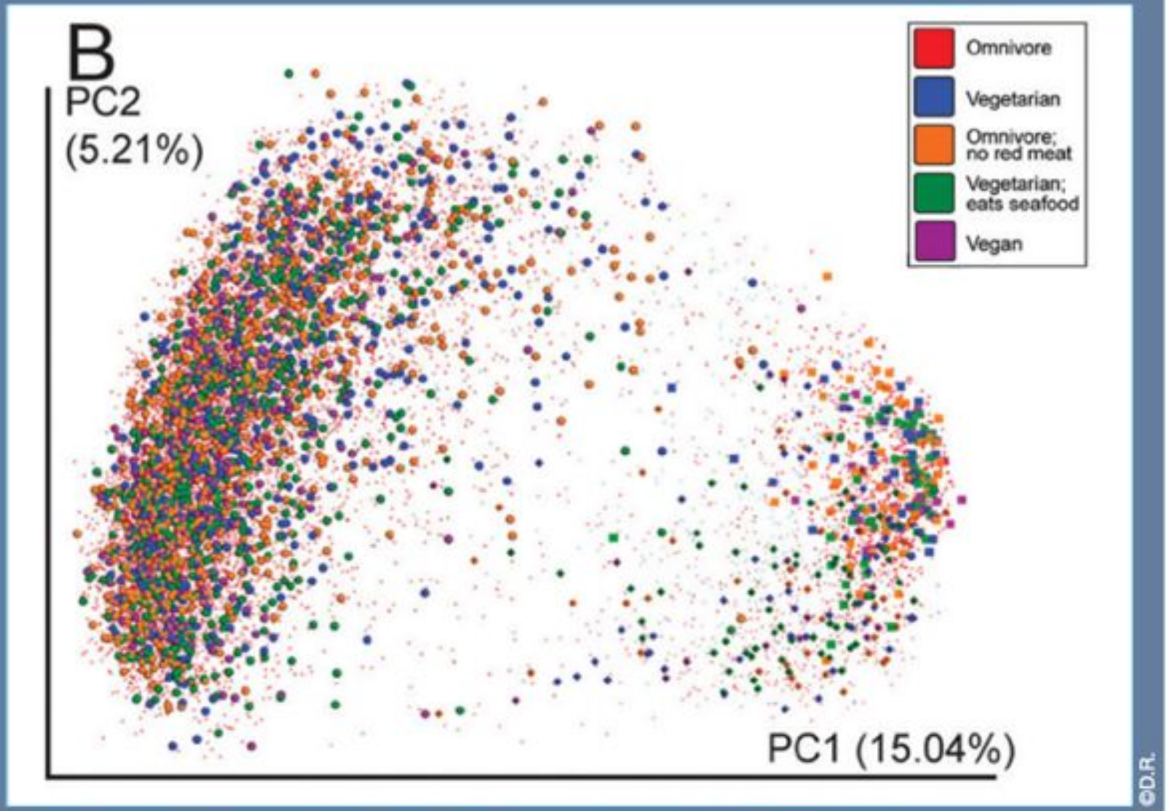
Fecal metabolomic analysis suggested potential amino acid-related pathways linking gut microbiota to inflammation. This study suggests that gut microbiota may underlie the predisposition of normal individuals to severe COVID-19.



Gou W, Fu Y, Yue L, et al. Gut microbiota may underlie the predisposition of healthy individuals to COVID-19. *Public and Global Health.* April 2020. doi:10.1101/2020.04.22.20076091
Zuo T, Zhang F, Lui GCY, et al. Alterations in Gut Microbiota of Patients With COVID-19 During Time of Hospitalization. *Gastroenterology.* May 2020. doi:10.1053/j.gastro.2020.05.048

Diet Matters for Diversity

Data from the American Gut Project has revealed that the diversity of plants that a subject consumes is associated with microbial diversity. Consuming more than 30 types of plants per week and consuming more vegetables and fruits was associated with a higher abundance of conjugated linoleic acid – which is generally related to reduced inflammation and cardiovascular disease – and a reduction in certain antibiotic resistance genes. The fact that microbial communities tend to group by macronutrient and micronutrient intake levels in a person diet rather than by diet type highlights the contribution of dietary nutrients in regulating gut microbial metabolism.

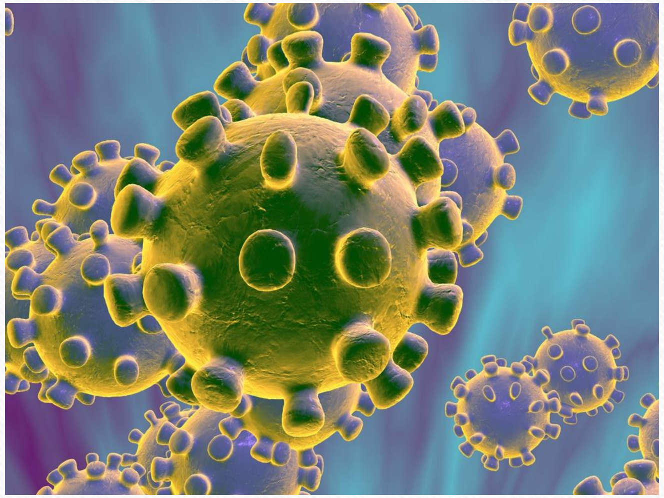


The gut microbiota communities failed to group together by diet type.
Source: McDonald D et al, mSystems 2018 ; 3(3) : e00031-18.

Get your 30!

onion	mushroom	avocado	heirloom tomato	basil	lentils	sun-dried tomato	cauliflower
broccoli	celery	rosemary	potato	red beans	peas	walnuts	dates
pistachio	cashews	artichoke	white corn	black beans	spinach	pepper	green beans
	soy	cinnamon	apple	banana	blackberries	carrots	

Vaccines



Types of Vaccines

Killed/Inactivated

Attenuated

Recombinant

Toxin

RNA/DNA

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Inactivated/Killed

Microbe is killed with heat and/or formaldehyde

Examples of vaccines using killed microbes

- Salk Polio vaccine, HepA, Flu (some), Rabies

Disadvantages

- Don't provide as good of immunity; Usually need boosters
- Often require an adjuvant – Aluminum hydroxide, Aluminum phosphate, etc

Live Attenuated

Pass microbe through several species to create a weakened form of pathogen

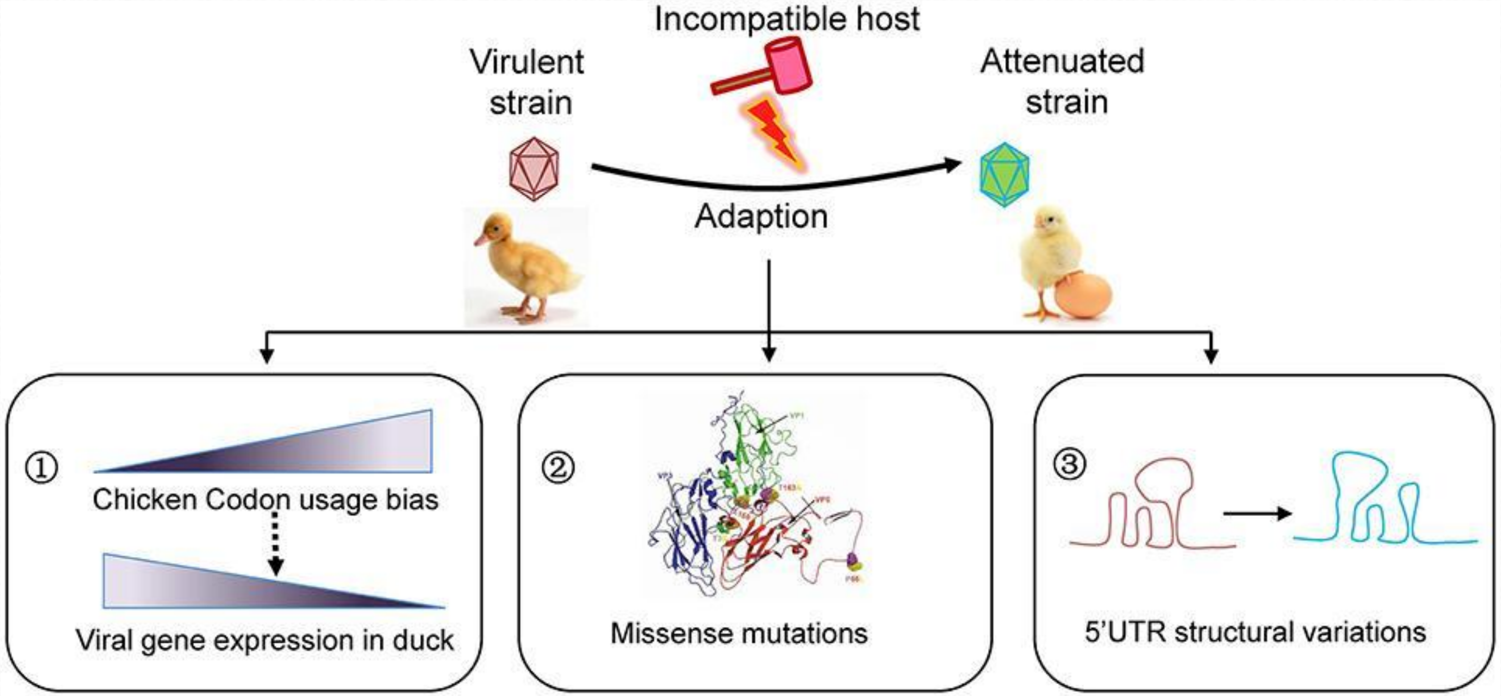
Examples of Attenuated Vaccines

- MMR, Rotavirus, Smallpox, Chickenpox, Yellow Fever, Sabin Polio vaccine

Disadvantages

- Because these are the strongest vaccines, provide vigorous immunity – and may have side effects
- Can revert to active form of pathogen

Attenuated Vaccines



Recombinant

Synthesized versions of proteins of the pathogen

Examples of Recombinant or sub-unit vaccines

- HiB, HepB, HPV, Pertussis, Pneumococcal, Meningococcal, Shingles

Disadvantages

- Not very immunogenic so requires adjuvants and booster shots

Toxin/Toxoid

Use toxin from the pathogen

Examples of toxin vaccines

- Diphtheria, Tetanus

Disadvantages

- More immunogenic than recombinant, but still need booster shots

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DNA/RNA

DNA or RNA from microbe used

Examples

- There are none currently on the market
- Vaccines work great in animals, but haven't been effective in humans

Disadvantages

- While these are inexpensive vaccines, and work in animals, they haven't successfully generated T cell immunity in humans

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Recombinant Vector

DNA from a protein (like a spike protein) is put into a less-pathogenic microbe

- Example: TB protein put into Listeria; HIV spike put into adenovirus

Examples

- There are none currently on the market

Disadvantages

- Adding the protein can promote significant changes in the less-pathogenic microbe

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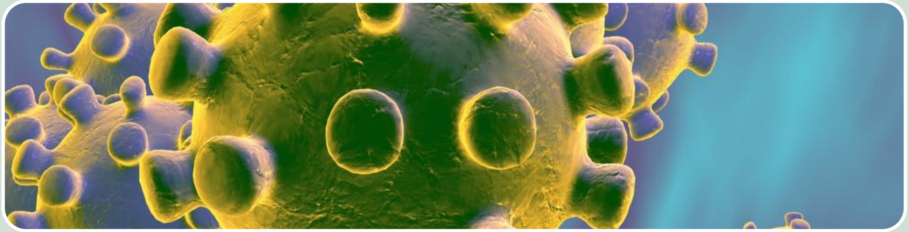
Immune Response to Vaccines



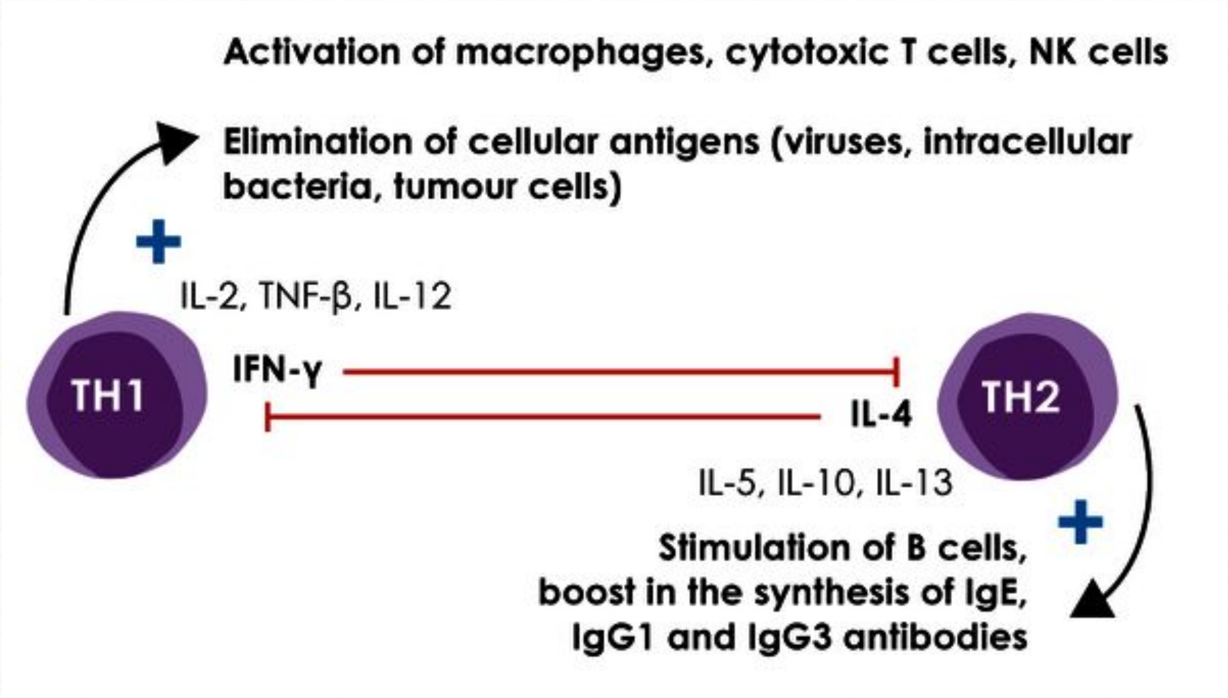
Th1 – CD8 T cell Response

Th2 – Antibody / Humoral Response

Immune Response to Microbes

Th1 – CD8 T Cell Response	Th2 – Antibody Response
Best for Intracellular Pathogens (Viruses; Intracellular Bacteria)	Best for Extracellular Pathogens (Preventing uptake; Worms)
Difficult to measure – requires isolating T cells from lymph nodes	Easier to measure – look at antibody titers
Cytokines: IFNgamma	Cytokines: IL-4, IL-5, and IL-13
Antibody Isotype: IgG2, IgG3	Antibody: IgG1, IgE, IgA

Immune Response to Microbes



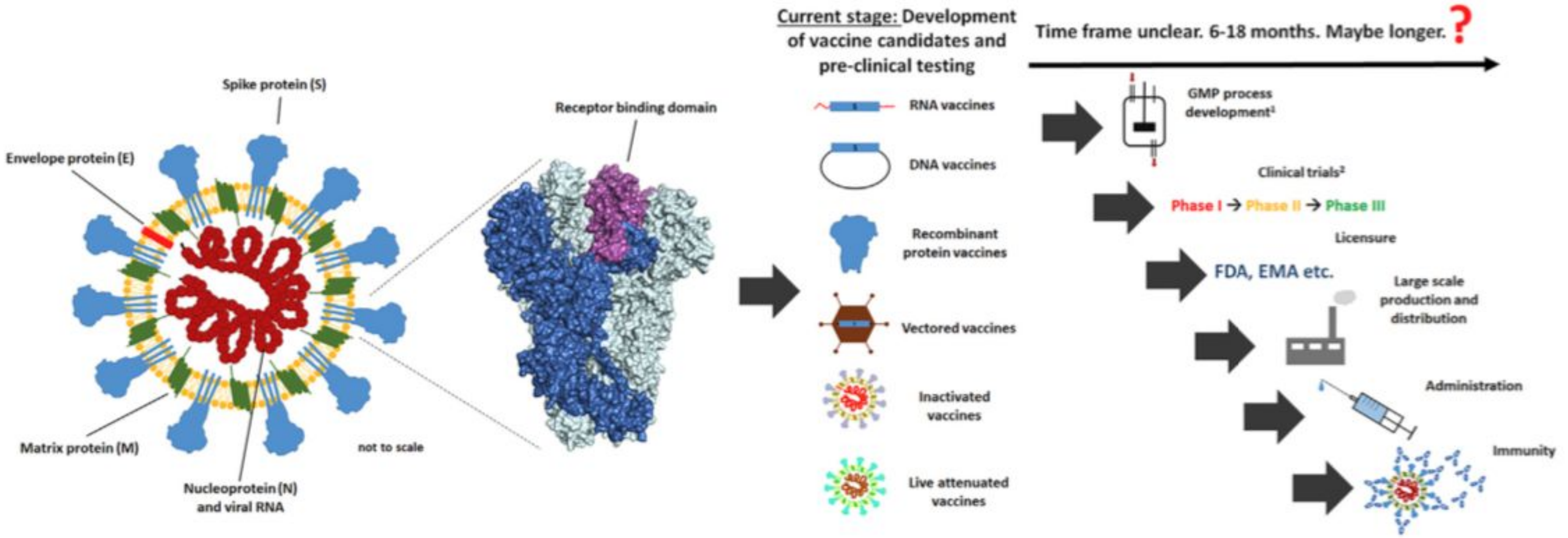


Figure 1. Overview of Potential SARS-CoV-2 Vaccine Platforms

The structure of a coronavirus particle is depicted on the left, with the different viral proteins indicated. The S protein is the major target for vaccine development. The spike structure shown is based on the trimeric SARS-CoV-1 spike (PDB: 5XL3). One trimer is shown in dark blue, and the receptor binding domain, a main target of neutralizing antibodies, is highlighted in purple. The other two trimers are shown in light blue. SARS-CoV-2 vaccine candidates based on different vaccine platforms have been developed, and for some of them, pre-clinical experiments have been initiated. For one mRNA-based candidate, a clinical trial recently started to enroll volunteers shortly (ClinicalTrials.gov: NCT04283461). However, many additional steps are needed before these vaccines can be used in the population, and this process might take months, if not years. [1]For some candidates, cGMP processes have already been established. [2]Clinical trial design might be altered to move vaccines through clinical testing quicker.

Major COVID-19 vaccine development programs

Consortium	Candidate vaccine	Reference
Whole virus vaccines		
Janssen (Johnson & Johnson)	Adenovirus-vectored vaccine using AdVac® and PER.C6® technology	[10]
Codagenix/Serum Institute of India	Live-attenuated vaccine	[11]
Subunit vaccines		
University of Queensland/CEPI	Protein-based vaccine using Molecular Clamp platform	[12]
Novavax	Recombinant nanoparticle technology	[13]

Chen WH, Strych U, Hotez PJ, Bottazzi ME. The SARS-CoV-2 Vaccine Pipeline: an Overview [published online ahead of print, 2020 Mar 3]. *Curr Trop Med Rep*. 2020;1-4. doi:10.1007/s40475-020-00201-6

Subunit Vaccines

Clover Bipharmaceuticals	S-trimer recombinant protein using Trimer-Tag technology	[14]
Baylor College of Medicine, Fudan University, New York Blood Center, Univ Texas Medical Branch	Coronavirus RBD protein-based vaccine	[15]
Vaxart	Oral recombinant protein vaccine using VAAST platform	[16]
Nucleic acid vaccines		
Inovio/Beijing Advaccine Biotechnology Co./CEPI	DNA vaccine (INO-4800, based on INO-4700 MERS vaccine)	[17]
Moderna/NIH/CEPI	mRNA vaccine	[18]
CureVac/CEPI	mRNA vaccine	[19]

Chen WH, Strych U, Hotez PJ, Bottazzi ME. The SARS-CoV-2 Vaccine Pipeline: an Overview [published online ahead of print, 2020 Mar 3]. *Curr Trop Med Rep*. 2020;1‑4. doi:10.1007/s40475-020-00201-6

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Vaccine Progress (Oct 29 2020)

NIH has partnered with more than 18 biopharmaceutical companies to accelerate development of drug and vaccine candidates for COVID-19 (ACTIV)

ACTIV says human trials could take 1-2 years

Effectiveness of vaccines

- US FDA says vaccines will need to be 50% effective or better
- EU says they will license vaccines less than 50% effective

COVID Vaccine Tracker

- If you want to follow along:

https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker

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Notice What is Missing

Inactivated vaccines

- Past attempts at inactivated vaccines led to increased infectivity

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Advantages and Disadvantages

Attenuated/ Vectored

- Will likely generate best immune response; Stimulate TLR 3, 7, 9
- If people have side-effects, they could be lung related; vector could target wrong organ system
- Takes longer to make

RNA

- Currently generating neutralizing antibodies
- Antibodies may prevent infection
- T cell response needed for full-protection

Subunit

- Safe for at-risk populations
- Will likely require an adjuvant and boosters

Additional Thoughts

Stockpiling
- Major coronavirus infection every 10 years

Shortage of glass vials and rubber stoppers
- Preloaded syringes;
- Preservatives

Past CoV vaccines
- Increased infectivity

Summary


Baseline health matters


Immune response to COVID – stuck in inflammation (IL-6)


Promising treatments


Vaccines must target a T cell response

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Thank You!

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