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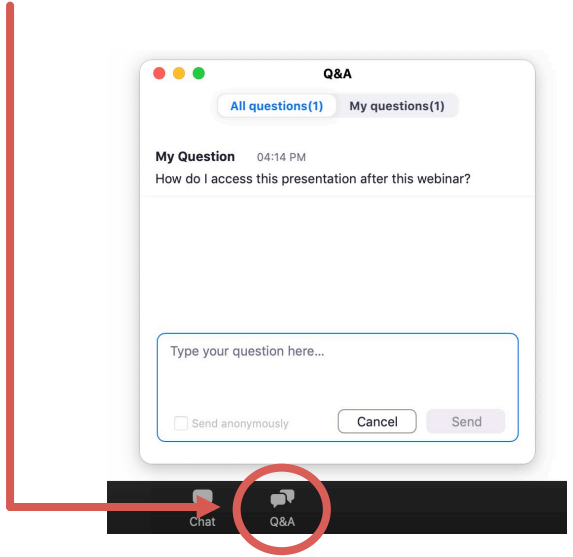

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The Future of COVID-19

Vaccines and the Trajectory of Care

Paradigm

Today's Speakers

Michael Choo, MD, MBA, FACEP, FAAEM, CMRO
Chief Medical Officer
Paradigm

Kathy Galia, RN, BSN
General Manager,
Clinical Solutions
Paradigm

Lawrence Lottenberg, MD, FACS
Medical Director
Paradigm

Steven M. Gordon, MD
Chairman of the Department of
Infectious Diseases
Cleveland Clinic Foundation

Objectives

Discuss the current state of COVID-19 and the ever-changing societal impact

Review FDA approved emerging treatments, such as monoclonal antibodies and vaccines

Understand the long-term effect of COVID-19—long haulers and permanent organ impairments

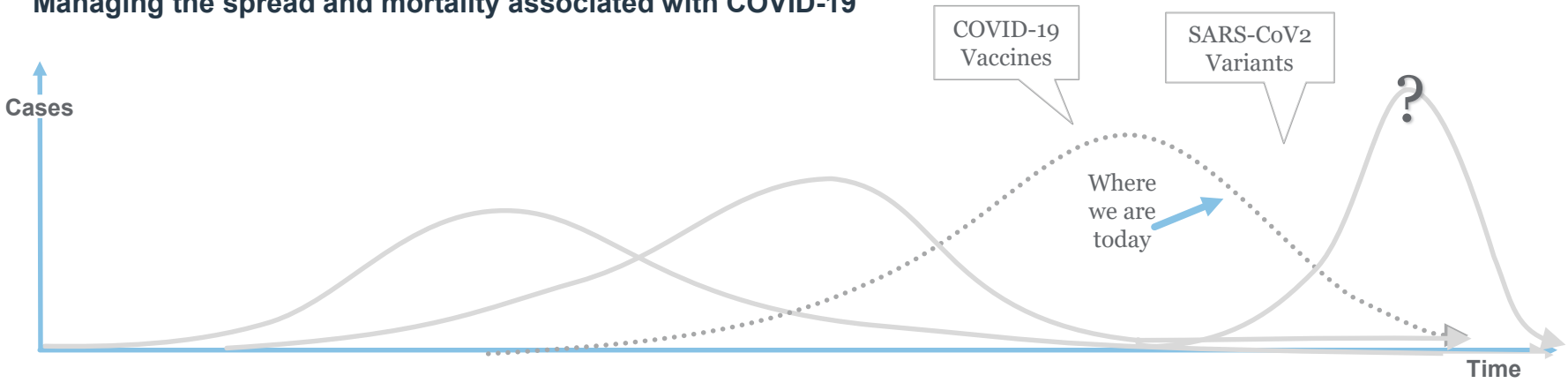
Present COVID-19 case studies

Current State of COVID-19

The ever-changing societal impact

Our Nation Faces One of the Great Challenges of Our Generation

Managing the spread and mortality associated with COVID-19



Emerging

- Initial cases identified
- Community spread begins
- No disruption to health care system
- Providers still accessible
- No impact on workers' comp claims

Rapid escalation

- Rapid growth in positive cases
- Severe access to care challenges
- Delivery through non-traditional sites of care
- Contraction in medical supply chain
- Evolving coverage positions for work related COVID-19 claims

Undulating recovery

- Mixed compliance with safety precautions
- Vaccine roll-out delays
- COVID-19 variants
- More testing, surveillance, and return to work protocols
- Recovery and management of severe COVID-19 claims ongoing

Overview

Graphic distribution

- Above 115 million confirmed cases of COVID-19 globally with over 2.5M deaths
- US total cases with 29M and approximately 527K deaths
- Worldwide recovered exceeds 90M while US with 21M

Care trajectory

- Nothing needed to ICU/Critical Care
- Multi-organ dysfunction
- Long-term post-COVID symptoms

Period of infectivity

- Period of infectiousness -“front loaded” and exposure type
  - 2.3 days prior to symptom onset, and up to seven days post symptoms
  - Prolonged close contact indoors
- Asymptomatic transmission confirmed
- Prolonged viral detection does NOT indicate prolonged infectiousness

Immunity

- National Institute of Health study suggests that virus induced immunity is protective in short term—eight months
- Further research is needed to determine long-term immunity
- Reinfections are a reality—but rare
- Multiple vaccines approved for use

Emerging Outpatient Treatments

Monoclonal antibodies

Monoclonal Antibody in COVID-19

Monoclonal antibodies against SARS-CoV-2 spike protein has been approved for treatment of mild infection in patients at high risk for severe outcomes

Criteria for use

Outpatient with positive SARS-CoV-2 viral test *and*

Symptoms for ≤ 10 days AND at least one of the following:

- ≥65 years of age
- BMI ≥ 35
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease
- Currently receiving immunosuppressive therapy
- ≥ 55 years of and one of the following:
  - Cardiovascular disease
  - Hypertension
  - COPD/other chronic respiratory disease that have required hospitalization in the past year

Exclusions

- Requiring hospitalization due to COVID-19
- Requiring oxygen therapy due to COVID -19
- Required an increase in baseline oxygen flow rate due to COVID-19 in those with chronic oxygen therapy due to underlying non-COVID-19 related comorbidity

Summary of Monoclonal Antibody Therapy for Outpatients with COVID-19

Treatment	Hospitalization/ED visits– ALL (*n*)	Hospitalization/ED visits-- HIGH RISK (*n*)
Bamlanivimab		
Placebo	6% (9/156)	10% (7/69)
Pooled doses	2% (5/309)	**3% (4/136)**
Casivirimab/Imdevimab		
Placebo	6% (6/93)	9% (7/78)
Pooled doses	3% 96/182)	**3% (4/151)**
Bamlanivimab/Etesevimab		
Placebo	7% (36/517)	10% (7/68)
Pooled doses	2% (11/518)	**3% (1/38)**

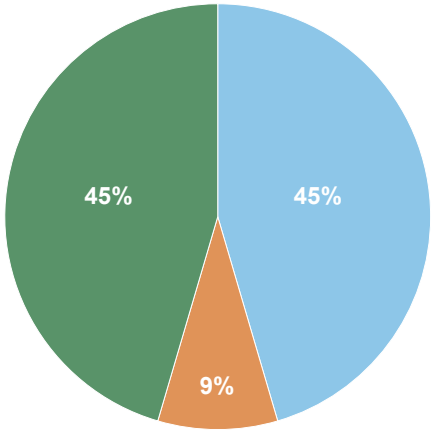
Source: Chen: https://www.nejm.org/doi/full/10.1056/NEJMoa2029849; Gottlieb: https://jamanetwork.com/journals/jama/fullarticle/2775647; Weinreich: https://www.nejm.org/doi/full/10.1056/NEJMoa203500

MaB Therapy for COVID-19 at the Cleveland Clinic

Outcomes for 180 outpatients

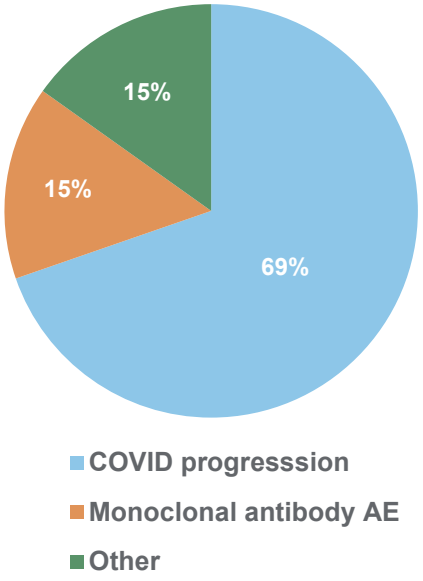
Hospitalization/ED visit 13.3%

ED Visit Only (n=11)



Median time from infusion to ED visit: 7.2 days (2.5, 11.5)

Hospital Admission (n=13)



Median time from infusion to hospital admission: 1.6 days (0.5, 4.3)

Emerging Treatments

Vaccines

COVID-19 Vaccine Platforms: Developed at the “Speed of Science”

Platform	Upside	Downside	Examples
RNA (genetic)	Simple to produce No risk of genomic integration	Delivery challenging Unproven	**Moderna, Pfizer/BioNTech**
Viral vectors	Strong immune response Durable response	Pre-existing immunity against vector; adverse reactions	Astra-Zeneca, **J&J**, “Sputnik 5”, CanSino
Protein/subunits	High safety Production quick	Require adjuvant Less immunogenic	Novavax, Sanofi Pasteur
Attenuated virus	Entire viral repertoire Very strong cytotoxic response	Risk of reversion Transport/storage more challenging	Not yet in clinical trials
Inactivated virus	Easily manufactured Very strong immune response	Possible Th2 bias	SinoPharm (Wuhan and Beijing)
DNA (genetic)	Simple to produce Stable	Less Immunogenic Delivery challenging	Inovio
Virus-like particle	Safety Immunogenicity Flexibility of production	Enveloped VLP more challenging to produce Small track record	Medicago
T-cell based	Easily manufactured Storage/transport simple	Little track record Ignores antibody role	Not yet in clinical trials

Thresholds for Immunity (Vaccine Efficacy)

Protection against symptomatic infections

Efficacy is primary endpoint in all trials defined as preventing “infection”

Protection against severe symptoms

Prevention of COVID-19 and hospitalizations/ deaths

Protection against transmission

“Sterilizing immunity”

COVID-19 Vaccine Pipeline and FDA Emergency Use Authorization Approval

	mRNA Vaccines		Adenovirus Vector		Recombinant /Adjuvant
Product	**mRNA 1273**	**BNT162b2**	ChAdOx1/ AZD1222	**AD26.CoV2.S**	NVX-CoV2373
Company	**Moderna/ NIAID**	**BioNTech/ Pfizer**	Oxford/ AstraZeneca	**J&J**	Novavax
Series	**0, 28 days**	**0, 21 days**	0, 28 days	**1-dose**	0, 21 days
Ages studied	**≥ 18 years**	**12-85 years**	≥ 18 years**	**≥ 18 years**	18-84 years
Phase of development	**FDA EUA approved**	**FDA EUA approved**	Phase III	**FDA EUA approved***	Phase III
Doses per vial	**10**	**5**	NR	**5**	NR
Storage	**-20°C**	**-70 ± 10 °C**	-20°C or Fridge	**Fridge**	Fridge
Stability	**Fridge: 7-14d RT: 6 hours**	**Fridge: 5d RT: 6 hours**	NR	**Fridge: 3 mo RT: 6 h**	NR

*FDA EUA approval 2/27/2021

- Phase III expanded to include patients > 12 years of age and patients with controlled HIV, Hepatitis B, Hepatitis C
- Phase II-III in pediatric patients 5-12 years in UK
- Approval to enroll patients 12-18 years of age and pregnancy

Source:NCT04470427 (Moderna COVE trial), NCT04368728 (Pfizer Phase 1/2/3), NCT04516746 (AstraZeneca Phase III), NCT04505722 (Janssen ENSEMBLE trial), Novavax Press Release

mRNA (Genetic) Vaccine Platform

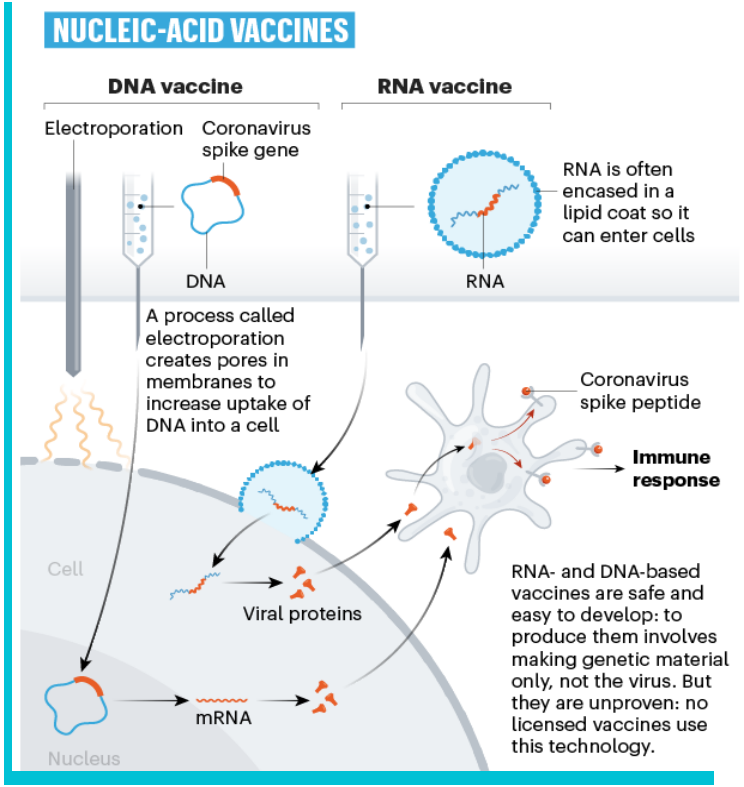
Advantages

- Non-infectious and non-integrating
- Scalable production
- Generates humoral/cellular immunity
- Modifiable to adjust to variant of concern

Disadvantages

- First-in-class
- Fastidious handling
- Cold storage requirements

mRNA products are not interchangeable



Source: Vitruvian Partners daily update

mRNA Vaccines Are Safe

First Month of COVID-19 Vaccine Safety Monitoring—United States December 14, 2020-January 13, 2021

TABLE 2. Percentage of v-safe enrollees who completed at least one survey (N = 1,602,065) with local and systemic reactions reported for day 0–7 and for day 1 after receiving Pfizer-BioNTech and Moderna COVID-19 vaccines — v-safe,* United States, December 14, 2020–January 13, 2021

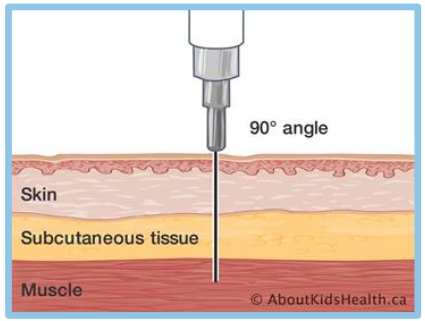
	Percentage of v-safe enrollees reporting reactions			
	Both vaccines	Pfizer-BioNTech vaccine		Moderna vaccine
Local and systemic reaction	Day 0–7	Dose 1, day 1	Dose 2, day 1	Dose 1, day 1
Injection site pain	70.9	72.9	79.3	78.1
Fatigue	33.5	21.9	53.5	25.1
Headache	29.5	17.5	43.4	19.9
Myalgia	22.9	14.7	47.2	18.3
Chills	11.6	5.5	30.6	8.4
Fever	11.4	5.8	29.2	8.2
Injection site swelling	10.8	6.2	8.6	12.6
Joint pain	10.4	5.3	23.5	7.3
Nausea	8.9	4.2	14.0	5.5

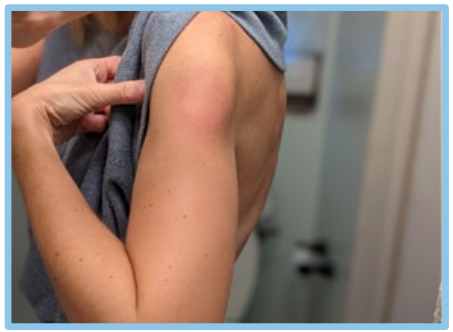
Anaphylaxis: Rate 2-11.1 per million doses administered

Source: Morbidity and Mortality Weekly Report

Reactogenicity

- Subset of reactions that occur after vaccination and are a physical manifestation of the inflammatory response to vaccination
- CDC does recommend treatment of symptoms, not prevention
- For some relief, CDC recommends people take an over-the-counter medicine such as acetaminophen or ibuprofen to alleviate symptoms





Source: https://www.aboutkidshealth.ca/

mRNA Vaccine

Israeli study shows was as effective (>90%) for a wide range of COVID-19 related outcomes across age groups as studies used to get FDA approval

596,618 in vaccinated cohort matched 1:1 in unvaccinated cohort

Estimated vaccine effectiveness against COVID-19 outcomes during three time periods*

Period	Documented Infection		Symptomatic Illness		Hospitalization		Severe Disease		Death	
	1-RR	Risk Difference	1-RR	Risk Difference	1-RR	Risk Difference	1-RR	Risk Difference	1-RR	Risk Difference
	% (95% CI)	No./1000 persons (95% CI)	% (95% CI)	No./1000 persons (95% CI)	% (95% CI)	No./1000 persons (95% CI)	% (95% CI)	No./1000 persons (95% CI)	% (95% CI)	No./1000 persons (95% CI)
14 to 20 days after first dose	46 (40-51)	2.06 (1.70-2.40)	57 (50-63)	1.54 (1.28-1.80)	74 (56-86)	0.21 (0.13-0.29)	62 (39-80)	0.14 (0.07-0.21)	72 (19-100)	0.03 (0.01-0.07)
21 to 27 days after first dose	60 (53-66)	2.31 (1.96-2.69)	66 (57-73)	1.34 (1.09-1.62)	78 (61-91)	0.22 (0.13-0.31)	80 (59-94)	0.18 (0.10-0.27)	84 (44-100)	0.06 (0.02-0.11)
7 days after second dose to end of follow-up	92 (88-95)	8.58 (6.22-11.18)	94 (87-98)	4.61 (3.29-6.53)	87 (55-100)	0.22 (0.08-0.39)	92 (75-100)	0.32 (0.13-0.52)	N/A	N/A

*Confidence intervals were estimated using the percentile bootstrap method with 500 repetitions. Estimates were calculated only for cells with more than 10 instances of an outcome across the two groups. NA denotes not available, and RR risk ratio.

Take home points:

Two doses provided increased effectiveness vs. single dose for all outcomes

B.1.1.7 variant estimated to be 80% of isolates in Israel at studies end

Source: Dagan N et al NEJM Feb 24 , 2021

Viral Vector Vaccines

Johnson and Johnson (J&J Ad25.COV2.S) EUA approved by FDA Feb 27, 2021

- The vaccine works by injecting a piece of DNA from the COVID-19 spike protein into a virus called an adenovirus, which is the type of virus that typically causes colds
  - The adenovirus has been modified so that it can carry the DNA segment, but not replicate inside the body and causeillness
- In the phase three clinical trial, the J&J vaccine was shown to be **66% effective** in preventing moderate and severe COVID-19 disease 28 days after vaccination
- The vaccine efficacy against moderate disease varied depending on the region studied, **ranging from 57% effective in South Africa to 72% effective in the U.S.**
- Overall, the vaccine was also **85% effective in prevention hospitalization** and **100% effective in preventing death**, 28 days after vaccination
- Advantages
  - Single shot
  - No additional ingredients (no adjuvants or preservatives)
  - Can be refrigerated and with shelf life of three months
  - Anticipated 100 million doses by June 1, 2021

Mutations, Variants of Concern (VOC), and Strains

Mutation: actual change in sequence

Variant: genomes that differ in sequence

Strain: variant with demonstrably different phenotype (e.g. impact on disease/transmission/diagnostics or therapeutics)

- **B.1.1.7 (UK)**
  - Emerged as the prevalent strain (more transmissibility) in SE England with spread to 60 other countries (perhaps 2% of strains in USA)
- **B.1.3.5. (South Africa)**
- **P.1 (Brazil and Japan)**
- **CAL.20C (California)**
- **B.1.526. (NYC)**

Source: Lauring A and Hodcroft E, JAMA Jan 6, 2021; Davies NG et al (UK); *MMWR Jan 15 2021

Vaccine Variants of Concern

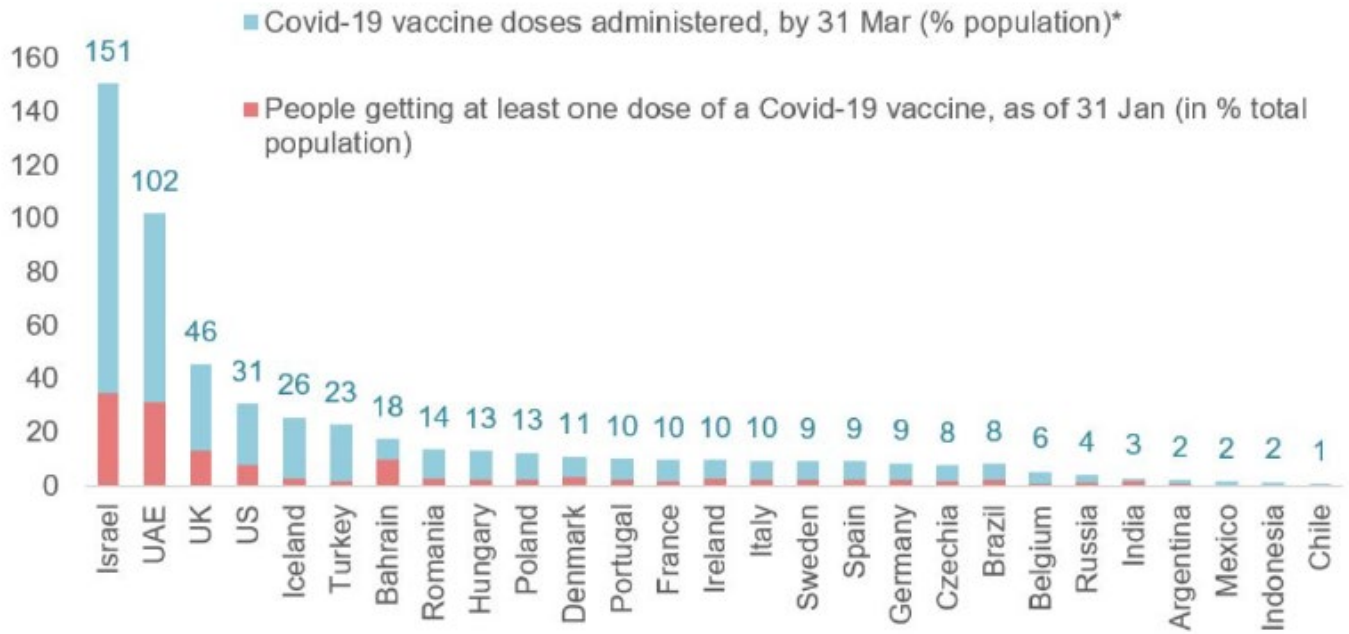
Dynamic and looming threat for vaccine efficacy and therapeutics

- mRNA vaccines appear to maintain protection against all key emerging VOC to date
- Adenovirus vaccine (Oxford) showed no protection against mild/modest infection in cohort in South Africa but J&J did show VE (64%) against moderate/severe illness
- mRNA boosters being constructed against B.131 VOC

Source: Vitruvian Partners daily update

Vaccine Administration

USA has administered most vaccines (almost 50 million), but Israel has highest % (>50%)



.Source: OurWorldinData, with estimates by BNP Paribas

Herd Immunity Metaphor

Starting a campfire: wet logs vs. dry logs

(R0> 1) with “dry logs”: without enough immunity in population, you can start and sustain a fire

(R0 < 1) with “wet logs”: if there is enough population immunity in population, you cannot start a fire

Forecasting the End of Pandemic

Defined as accepted as an ordinary fact of life

We will reach herd immunity (vaccine and/or natural infection)

- 60-90% of population

The pathogen will evolve to be less lethal

- e.g. OC43 strain of CoV, which was likely responsible for 1890 pandemic

The pathogen will disappear or become dormant

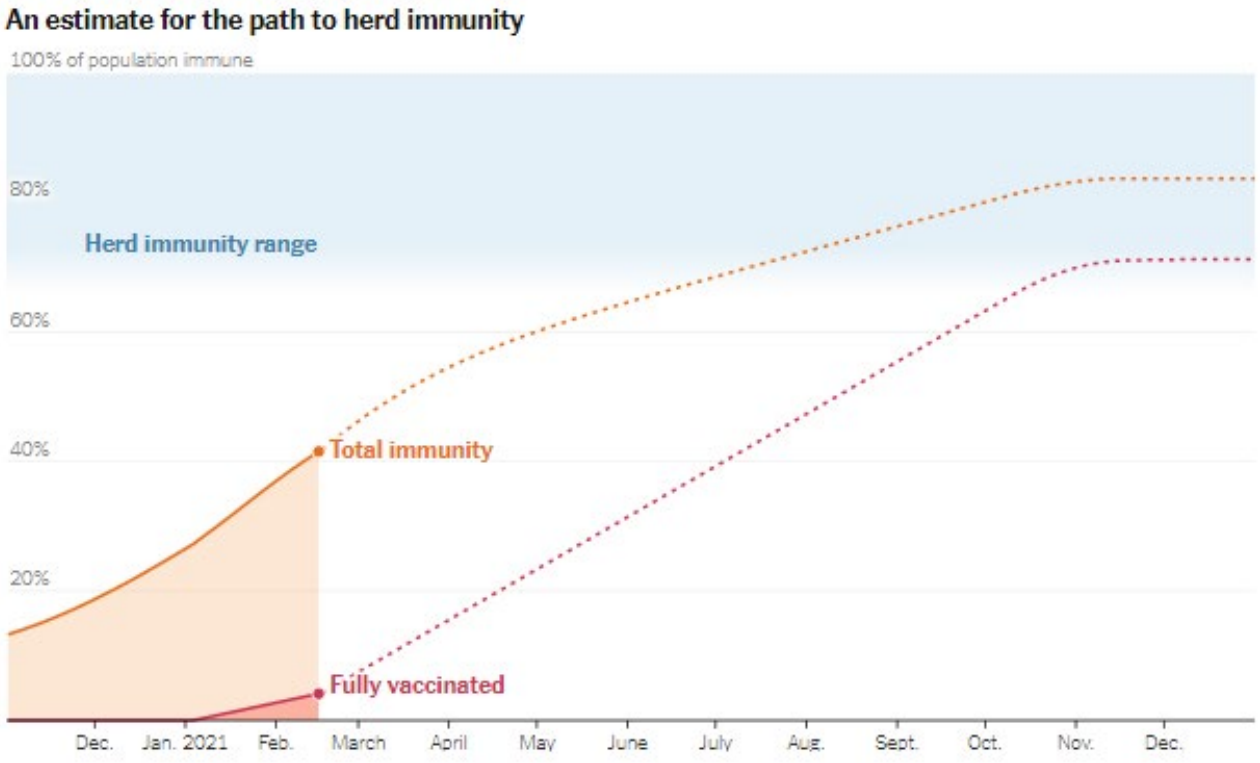
- e.g. SARS-CoV-1

Humans will evolve to be resistant (after a very long time)

Source: Kubler-Ross model 5 stages of grief: denial/anger/bargaining/depression/acceptance

Variables

Vaccine uptake, NPI, variants of concern, number of susceptibles



Source: New York Times

Understanding the Long-Term Effect of COVID-19

Where are we now?

Long-Term Complications

Persistent respiratory issues

- Long-term complications of ARDS
- Pulmonary fibrosis
- Pulmonary hypertension

Heart-related issues

- Post-myocarditis syndrome
- Post-myocardial infarction complications
- Congestive heart failure/pump failure
- Myofibrosis
- Arrhythmias
- Complications from delayed care

Neurological manifestations

- Encephalitis & seizures
- Stroke complications
- Spinal cord complications
- Post-intensive care syndrome (PICS)
  - Cognitive impairments
  - Critical care polyneuropathy

Mental health impact

- PTSD, anxiety, and depression
- Loss of control over their daily lives
- Psychosocial impacts on individuals workers and their families

The Long-Term Effects—Without Explicit Organ Dysfunction

Puzzling persistent symptoms

- Fatigue
- Muscle and body aches
- Shortness of breath
- Difficulty with “brain fog”
- Dysautonomia—tachycardia
- Malaise

Persistent Symptoms

Three to nine months after illness onset

177 questionnaire participants who contracted COVID-19

- Approximately **30% of participants** who were followed up for as long as nine months after illness reported **persistent symptoms**
- Overall:
  - **6.2% asymptomatic**
  - **84.7% outpatients with mild illness**
  - **9.0% had moderate or severe disease requiring hospitalization**
- Most common comorbidity:
  - **13.0% hypertension**

- **Persistent symptoms reported:**
  - 26.6% aged 18 to 39 years
  - 30.1% aged 40-64 years
  - 43.3% aged 65 years and older
  - Overall, 49 of 150 outpatients (32.7%): five of 16 hospitalized patients (31.3%) and one of 21 healthy participants (4.8%) in the control group reported at least one persistent symptom

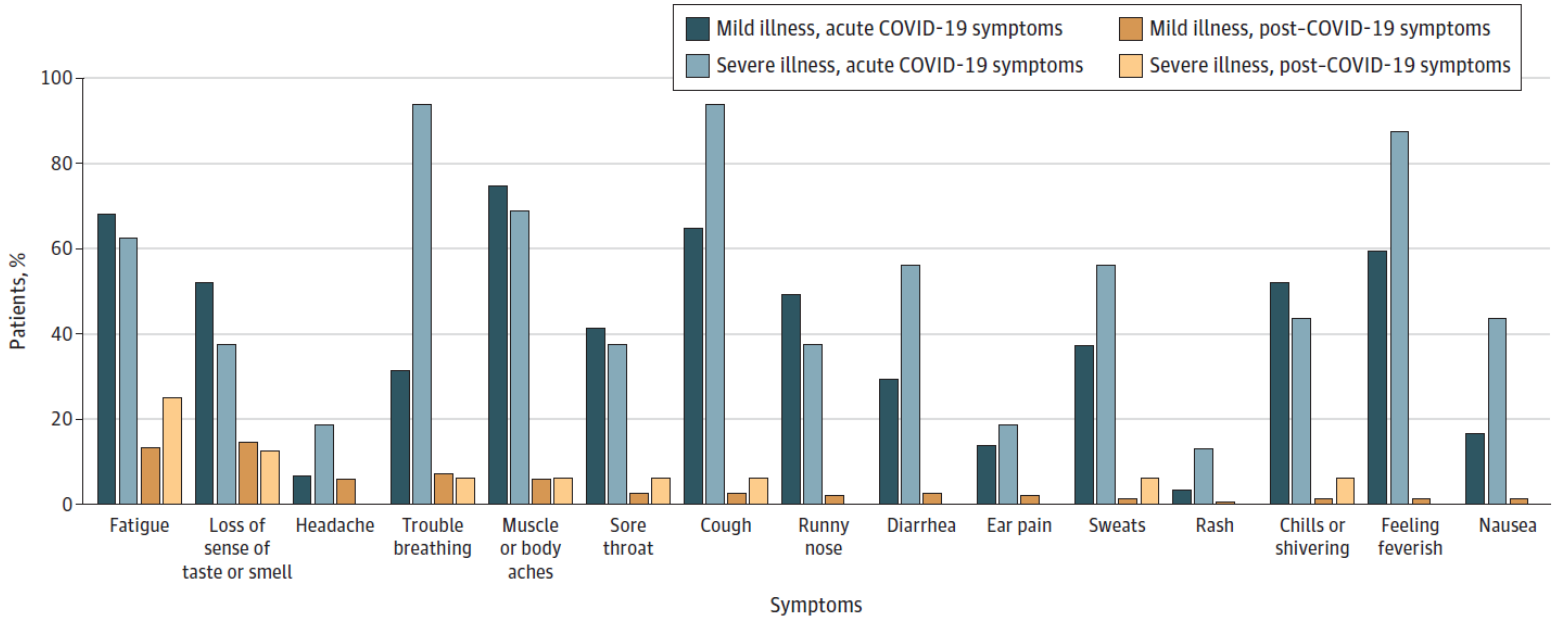
Source: Sequelae in Adults at 6 Months After COVID-19 Infection; 2021 Logue JK et al. JAMA Network Open

Persistent Symptoms

Three to nine months after illness onset

177 questionnaire participants who contracted COVID-19

Percentage of participants who reported COVID-19 symptoms during acute illness and at follow-up



Source: Sequelae in Adults at 6 Months After COVID-19 Infection; 2021 Logue JK et al. JAMA Network Open

More Than 50 Long-Term Effects of COVID-19

A systematic review and meta-analysis

Study details

- Prevalence of **55 long-term effects** were estimated
- 21 meta-analyses performed
- 47,910 patients included
- Follow-up time ranged from 14 to 110 days post-viral infection
- Age range was between 17 and 87 years
- **80%** (95% CI 65-92) of the patients that were infected with SARS-CoV-2 **developed one or more long-term symptoms**

The five most common symptoms were:

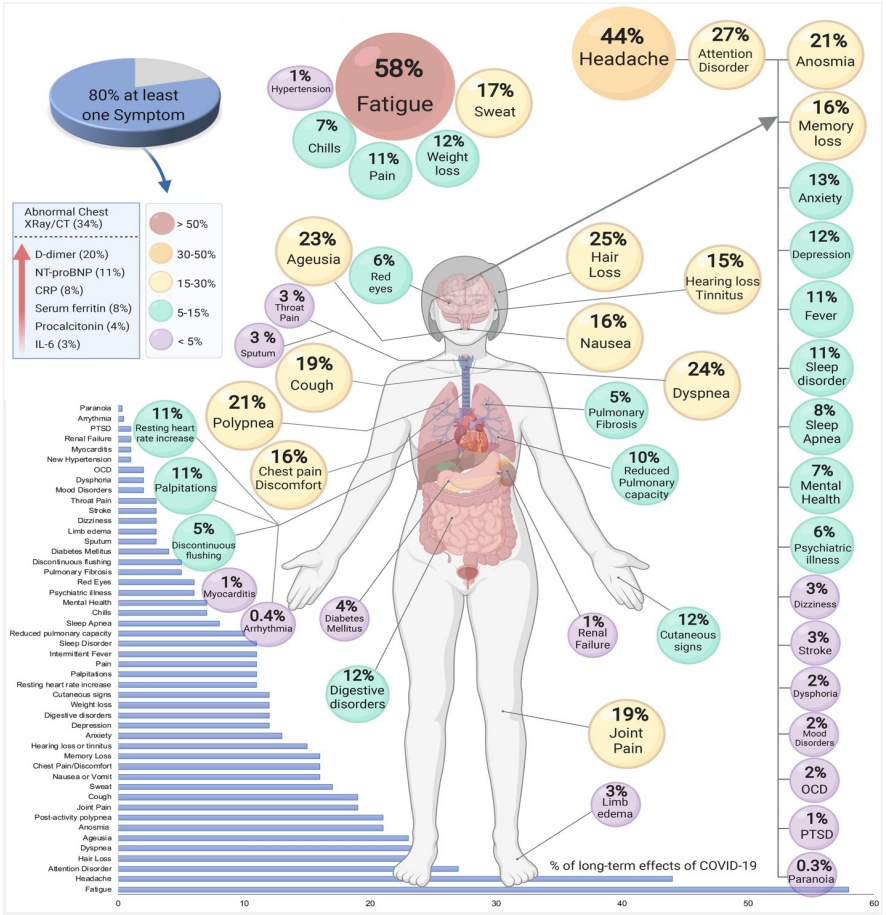
- Fatigue (58%)
- Headache (44%)
- Attention disorder (27%)
- Hair loss (25%)
- Dyspnea (24%)

Source: Emory University/Houston Methodist

More Than 50 Long-Term Effects of COVID-19

A systematic review and meta-analysis

Long term effects



Source: Emory University/Houston Methodist

Expert Comments

"These patients get sick very fast, and it takes a long time for them to heal. What's **not really well appreciated is how much rehab and how much recovery time these patients are going to need**."

-David Chong, MD

Medical director at New York–Presbyterian Hospital/Columbia University Medical Center ICU, who has been on the frontlines during the COVID-19 surge in NYC

"Some, but not all COVID-19 patients who develop ARDS may go on to develop **lung fibrosis**—scarring of the lungs—which may be permanent. Post-ARDS fibrosis typically is not progressive, but nonetheless can be severe and limiting. **The recovery period for post-ARDS fibrosis is approximately one year and the residual deficits persist.**"

-The Pulmonary Fibrosis Foundation

Survey at Eight Months Post COVID-19

50 respondents

- Identified **205 symptoms in 10 organs** linked to the virus
  - Including 66 symptoms traced over seven months
- Most commonly reported symptoms after six months:
  - **Fatigue (78%)**
  - **Post-exertional malaise (72%)**
  - **Cognitive dysfunction (55%)**
- Respondents who were sick six months after symptom onset experienced an **average of 13.8 symptoms**
- Most respondents had **not returned to full-time work** due to their health issues

COVID-19 Case Studies

Active COVID Case #1

Background

- 53-year old male (NY)
- Date of loss 5/22/2020, date of referral 8/4/2020
- Respiratory therapist
- Presented to ER with fever and shortness of breath
- Comorbidities include type II diabetes, asthma, GERD, and hypertension
- Diagnosis: COVID-19 and subsequent hypercoagulation
- CVA resulting in a C5, ASIA D, SCI
- Acute renal failure
- No family support
- Compensability not questioned

Paradigm Actions

- Reviewed medical records and compensability support
- Coordinated with providers to confirm injured worker had returned to baseline respiratory and renal functions by 8/10/2020
- Intervened on discharge plan routed from SNF to rehab
- Worked closely with the treatment team and injured worker to establish meaningful and measurable goals
- Provided psychosocial support/social worker
- Trialed a discharge home on 12/8/20; required coordination of readmission for additional acute rehabilitation

Current Situation

- Injured worker has been discharged to home (2/16)
- Home needs have been coordinated
- Injured worker able to ambulate short distances with a walker and perform activities of daily living
- Continent bowel and bladder
- Psychosocial support ongoing
- Lifetime expectancy

Active COVID Case #2

Background

- 32-year old male (NY)
- ER intake coordinator
- Date of loss/exposure 3/30/2020
- Presented NY ER 3/30/20 with fever, sweats, cough, chest tightness
- Diabetes type II
- Diagnosis: COVID-19, ARDS
- Vent support
- Hypercoagulation/ blood clot, infarcted spinal cord while vented
- C-4 quadriplegic
- ICU 9 weeks
- COVID diagnosis accepted at onset
- SCI diagnosis initially under review

Paradigm Actions

- Completed initial medical record review
- Compensability decision support
  - Collaborated with the injured worker's attorney
  - Selected and arranged transfer to Shepherd Center in Atlanta, GA 6/9/20
  - Coordinated acute rehabilitation needs
  - Coordinated discharge to home
  - Provided family support and guidance

Current Situation

- Injured worker discharged to a fully handicap accessible apartment on 12/1/20
- Requires 12 hours of attendant care/12 hours skilled nursing care
- Injured worker continues to participate in physical and occupational therapy in the home setting
- Cognitively intact and able to direct care
- Decannulated and free of respiratory compromise
- Lifetime expectancy

Objectives

Discuss the current state of COVID-19 and the ever-changing societal impact

Review FDA approved emerging treatments, such as monoclonal antibodies and vaccines

Understand the long-term effect of COVID-19—long haulers and permanent organ impairments

Present COVID-19 case studies

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- CE for national nurse credit
- CCMC national credit

How to receive credit

- Attend the entire live webinar.
- Five poll questions will pop up during the webinar. **You must respond to at least three polls to receive credit.**
- After the webinar, you will receive an email from **ceuinstitute.net** with a credit submission link and an **evaluation that will need to be completed** to receive credit.

Note: CE credit will not be provided for webinar replay.

Thank you

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