COVID-19 and Pemphigus and Pemphigoid

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December 9, 2020

Overview

Speaker	Topic
Mary Tomayko, MD, PhD	**What have we learned since the last webinar?** **Transmission, “long-COVID”, second wave, testing, tracing, precautions, travel**
Emanual Mavarakis, MD	Risk factors for more severe COVID, pemphigus/pemphigoid medication concerns
Aimee Payne, MD, PhD	COVID treatments and vaccines
Panel discussion	Additional time for questions and answers

Updates: SARS-CoV2 transmission

Children

- Children can become infected and can transmit the virus
- Most children have mild disease compared with adults

Durable immunity and re-infection

- The duration of protection after *infection* is not established
  - An area of active research
- Immunity lasts at least 3 months post-infection in most cases
- Re-infection is uncommon but can happen
- We anticipate that vaccination will induce more reliable immunity than infection

Updates: Long COVID

Lingering, debilitating health issues that persist months after infection

- **Common**
  - Fatigue, Shortness of breath, cough, chest pain, joint pain
- **Others**
  - Difficulty thinking and concentrating (“brain fog”), depression, muscle pain, headache, intermittent fever, palpitations
- **More serious**
  - Stroke
  - Inflammation of the heart muscle, lung function abnormalities, acute kidney injury
  - Hair loss, smell and taste problems, erectile dysfunction
  - Sleep issues, difficulty with concentration, memory problems, depression, anxiety, changes in mood

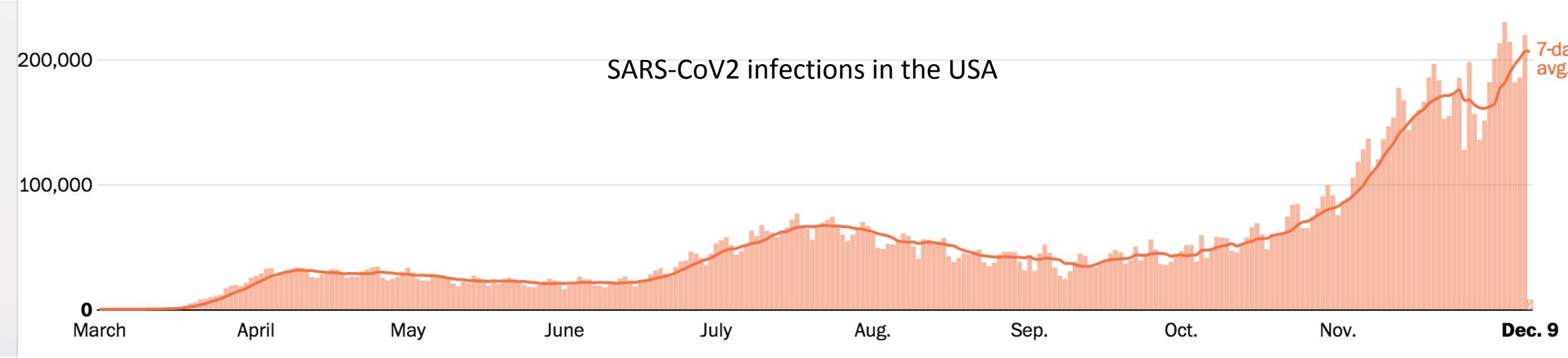
Risks for long COVID

- Unclear. Individuals with mild illness can experience persistent or late symptoms.
- RNA testing is negative as the infection has resolved

https://**www.cdc.gov/coronavirus/2019-ncov/long-term-effects**.html?ACSTrackingID=USCDC_425-DM42580&ACSTrackingLabel=Weekly%20Summary%3A%20COVID-19%20Healthcare%20Quality%20and%20Worker%20Safety%20Information%20%E2%80%93%20November%2016%2C%202020&deliveryName=USCDC_425-DM42580

Meeting the challenge of long COVID. *Nature Medicine*, 26:2803. Dec. 7, 2020.

Second wave



- Widespread geographical areas affected, large case numbers, community spread
- Human behavior is the main cause
- Winter months – indoors
- Holiday season – social gathering, travel

- Timing, length – depend on human behavior

There is a wide range of COVID symptoms

Severe disease

Asymptomatic (up to 40%)

Fever greater than 99.9°F or chills
Cough
Shortness of breath or difficulty breathing
Fatigue
Muscle or body aches
Headache
New loss of taste or smell
Sore throat
Congestion or runny nose
Nausea or vomiting
Diarrhea

Is this just the common cold?

- Test
- Isolate
- Notify your doctor

COVID testing

Are you infected right now?

- ***RNA tests (PCR) ***
  - Test for presence of viral genetic material, RNA
  - Most common and currently most sensitive and specific
  - An at-home kit was recently given FDA emergency use authorization (Lucira)
- Antigen tests
  - Test for viral proteins
  - Less sensitive than RNA tests.

Were you infected in the past?

- Serological (antibody) tests
  - Many versions. Sensitivity and specificity vary.

https://www.fda.gov/consumers/consumer-updates/coronavirus-disease-2019-**testing-basic**s
https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-**fda-authorizes-first-covid-19-test-self-testing-home**

Contact tracing

What have we learned from contract tracing?

- Masking, PPE, social distancing are effective
- Higher risk: indoor dinning, bars, indoor/contact sports
- Lower risk: school with masks, social distancing

Contact tracing is increasingly more difficult and less effective

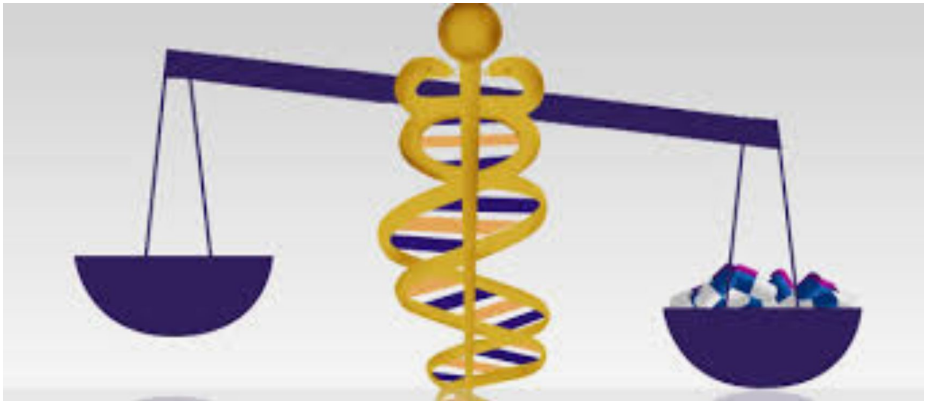
- Community spread
- Large numbers of new diagnoses
- Open restaurants, bars, workplaces, social events, etc.

Protecting against infection

Transmission: Airborne droplets and aerosols in contact with eyes, nose, mouth

- Masks, eye protection, hand washing
- Social distancing
- Gather outdoors in small groups
- Isolate if you have a possible exposure or symptoms

Travel



Recommended: Drive, bike, walk

Caution: Bus, train, airplane

- Is the travel essential?
- Rates of COVID-19 (community of origin, destination, transit points)
- Community adherence to CDC recommendations about masking, social distancing, isolation of infected individuals, availability of testing
- Your personal ability to protect yourself (PPE)
- (Airplanes) COVID testing of passengers

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Factors Associated with Hospitalization in Rheumatic Diseases (600 patients)

Characteristic	Odds Ratio	P-value
Female	0.83	0.39
Age	**2.56**	**<0.01**
Common comorbidities	**1.86**	**<0.01**
Heart disease	**2.48**	**<0.01**
Lung disease	**2.61**	**<0.01**
Diabetes	**3.02**	**0.02**
Kidney disease		
Prednisone-Equivalent	Ref	--
None	1.03	0.91
1-9 mg/day	**2.05**	**0.03**
≥10 mg/day		

All reported odds ratios are multi-variable adjusted

- Trend toward more men hospitalized but not significantly different from women
- Older individuals and those with heart/lung/kidney disease or diabetes are at greater risk for hospitalization
- Prednisone doses greater than 10 mg per day are associated with greater risk of hospitalization

Gianfresco et al, Ann Rheum Dis 2020;79:859
Slide adapted from Zachary Wallace, MD

Selected Factors Associated with Death in Rheumatic Disease (3,729 patients)

Medication	Odds ratio (95% CI)		
Methotrexate	1	[Reference]	
Antimalarials	0.92	0.63	1.33
AZA, MMF, cyclophosphamide	**2.04**	**1.37**	**3.04**
Rituximab	**3.68**	**2.09**	**6.47**

Medication	Odds ratio (95% CI)		
No Glucocorticoids	1	[Reference]	
GC 1-10mg/day	1.44	0.99	2.10
GC > 10mg/day	**1.67**	**1.17**	**2.37**

- Drugs commonly used for pemphigus and pemphigoid treatment are associated with increased risk of COVID-19-related death, particularly azathioprine, mycophenolate, and rituximab

Unpublished data, Zachary Wallace, MD

Factors associated with COVID-19 death in the UK (17+ million patients)

Characteristic	Category	Hazard ratio
Age	18–39	0.06 (0.04–0.08)
	40–49	0.30 (0.25–0.36)
	50–59	1.00 (ref)
	60–69	2.40 (2.16–2.66)
	70–79	6.07 (5.51–6.69)
	80+	20.60 (18.70–22.68)
Sex	Female	1.00 (ref)
	Male	1.59 (1.53–1.65)
Body mass index	Not obese	1.00 (ref)
	30–34.9	1.05 (1.00–1.11)
	35–39.9	1.40 (1.30–1.52)
	≥40	1.92 (1.72–2.13)
Lung disease		1.63 (1.55–1.71)
Heart disease		1.17 (1.12–1.22)
Diabetes	With HbA1c < 7.5	1.31 (1.24–1.37)
	With HbA1c ≥ 7.5	1.95 (1.83–2.08)
Kidney disease	eGFR 30–60	1.33 (1.28–1.40)
	eGFR < 30	2.52 (2.33–2.72)
Liver disease		1.75 (1.51–2.03)
Organ transplant		3.53 (2.77–4.49)
Other immunosuppressive condition		2.21 (1.68–2.90)

Williamson et al, Nature, 584:430 (2020)

Animal Data

Survival and Inoculum dose

TABLE 1 Determining the 50% lethal dose and 50% infectious dose of MERS-CoV in hCD26/DPP4 transgenic mice[a]

Experiment	Challenge dose ($TCID_{50}$/mouse)	No. of deaths/no. of challenged mice (%)	Day(s) of death postchallenge	No. of infected mice/no. tested (%)[b]
1	10^6	8/8 (100)	4–6	NA
	10^5	4/4 (100)	5–7	NA
	10^4	4/4 (100)	5–8	NA
	10^3	4/4 (100)	6–10	NA
	10^2	8/8 (100)	6–12	NA
	10^1	5/8 (62.5)	8–13	ND
2	10	2/4 (50)	9, 10	2/2 (100)
	5	1/4 (25)	9	3/3 (100)
	2.5	0/4 (0)	NA	3/4 (75)
	1.25	1/4 (25)	10	3/3 (100)

[a] Estimated LD_{50} and ID_{50} are 10 and <1 $TCID_{50}$, respectively. NA, not applicable; ND, not determined.

[b] Infection was determined by analysis of the serum antibody response in neutralization and/or ELISAs.

Middle East Respiratory Syndrome

J Virol. 2015 Oct 7;90(1):57-67

Inoculum dose and protection

TABLE 2 MERS-CoV serum antibody titers in survivors of the initial challenge and their response to rechallenge

Initial challenge dose ($TCID_{50}$)	No. of survivors	Serum antibody responses[a]		No. of mice that died or showed wt loss on rechallenge/total no. of mice[d]
		Neutralizing antibody[b]	ELISA IgG antibody[c]	
10	2	<10, 10	800, 800	0/2
5	3	10, <10, 20	800, 400, 800	0/3
2.5	4	20, 20, <10, 20	400, 400, <100, 400	0/4
1.25	3	<10, 10, <10	400, 400, 400	0/3

[a] Antibody responses were determined at 21 dpi.

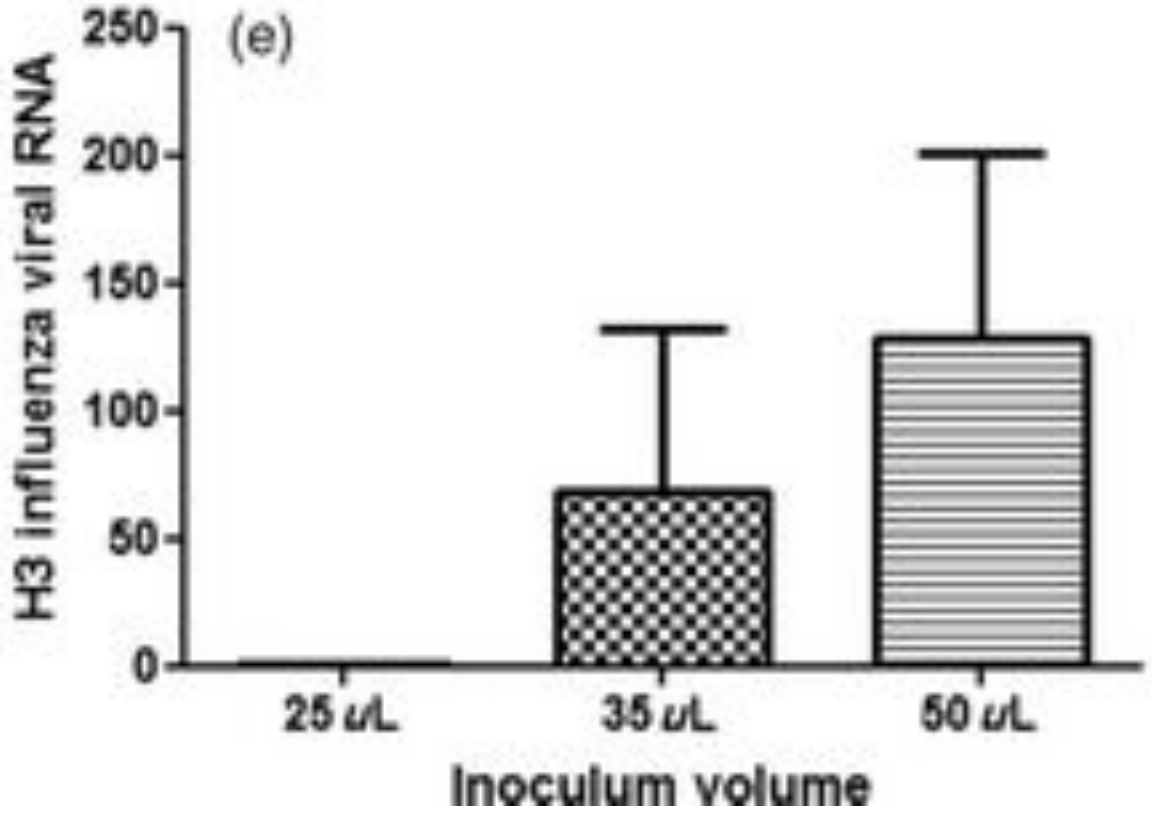
[b] Data represent the highest dilutions of sera that completely inhibited CPE formation in 100% of infected Vero E6 cultures (NT_{100}).

[c] Data represent the highest dilutions of sera with MERS-CoV S1-specific antibody with a mean optical density (OD) of ≥2 standard deviations (SD) greater than the mean measured for naive mice.

[d] Mice were rechallenged with 100 LD_{50} (10^3 $TCID_{50}$) of MERS-CoV at day 35 after the initial infection. Two of two simultaneously challenged naive Tg^+ mice exhibited severe (>20%) weight loss, and death occurred within 10 dpi.

J Virol. 2015 Oct 7;90(1):57-67

Survival and Inoculum volume

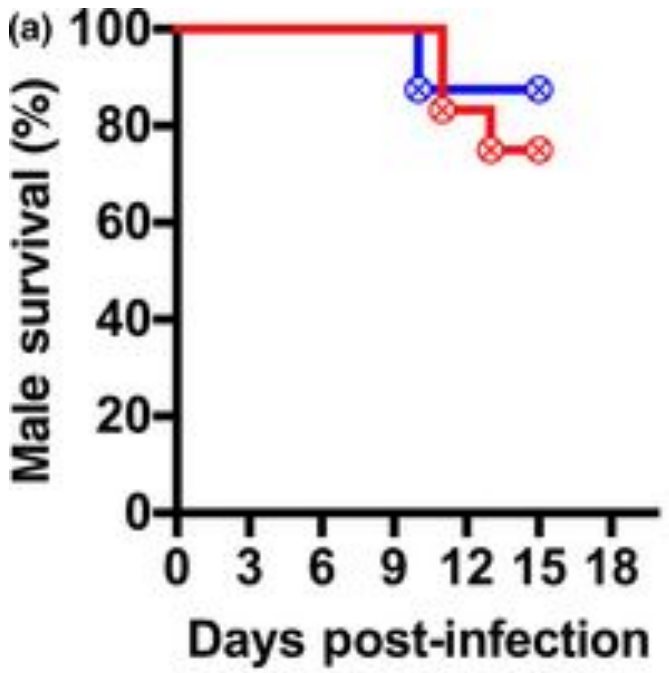


The virus inoculum volume influences outcome of influenza A infection in mice

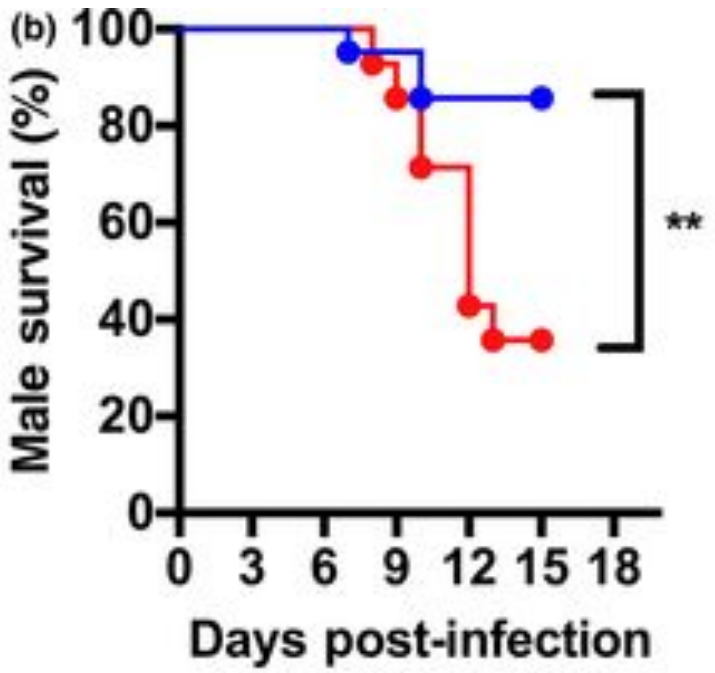
Lab Anim. 2013 Jan;47(1):74-7

Age, Survival and Inoculum volume

20 microleters



40 microleters

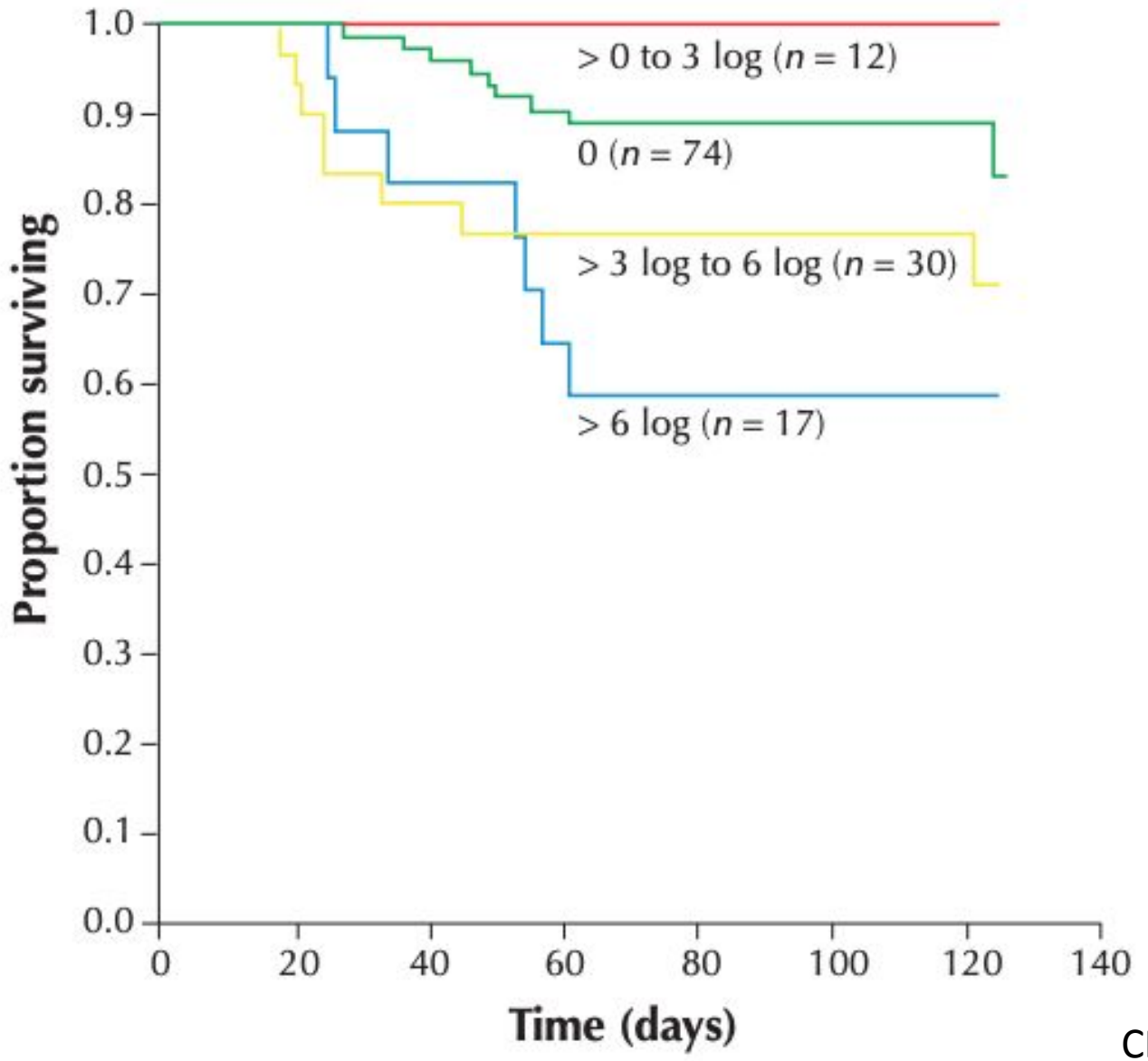


Influenza virus inoculum volume is critical to elucidate age-dependent mortality in mice

Aging Cell. 2019 Apr;18(2):e12893

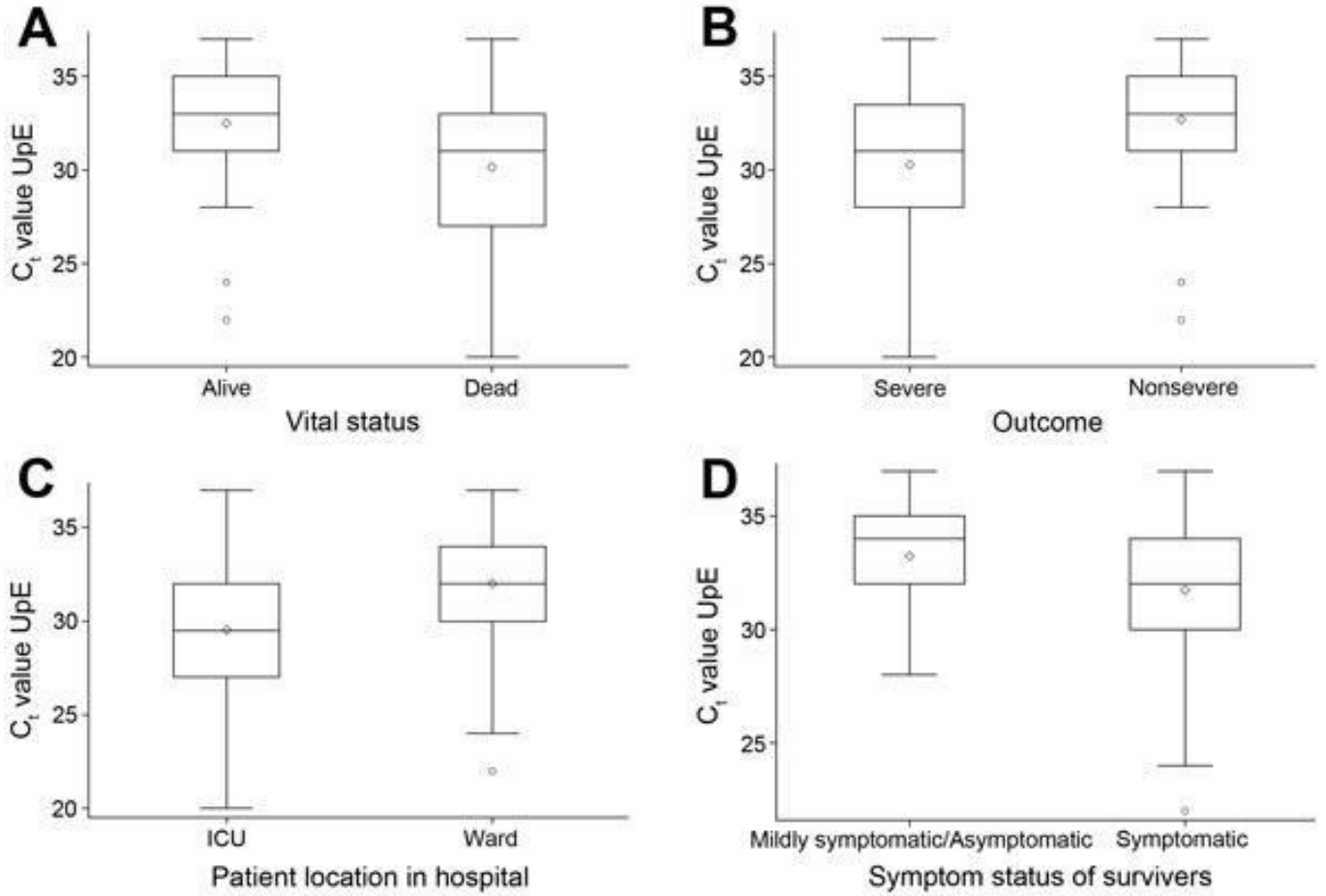
Human Data

Viral load and survival, SARS



CMAJ. 2004 Nov 23;171(11):1349-52

Viral load and survival, MERS-CoV



Association of Higher MERS-CoV Virus Load with Severe Disease and Death, Saudi Arabia, 2014

Emerg Infect Dis. 2015 Nov;21(11):2029-35

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Emergency Use Authorization

During public health emergencies, EUA allows the FDA to allow unapproved drugs to be used to diagnose, treat, or prevent serious or life-threatening diseases when there are no adequate, approved, and available alternatives.

Criteria for EUA are:

- Reasonable efficacy
- Benefits likely outweigh risks (both known and potential)
- There is no adequate, approved, and available alternative

https://www.fda.gov/media/142749/download

COVID-19 treatments: small molecules

Drug	Mechanism of action	Clinical use
Remdesivir	Inhibits viral replication	• Hospitalized patients age 12 or over • Study 1: Recovery time reduced from 18 to 11 days for severe disease. No effect for mild/moderate disease. Death at 29 days reduced from 15% to 11%. • Study 2: No effect on recovery or death • Study 3: 1.65 odds of improvement with a 5-day course; 1.31 odds with 10-day (latter not statistically significant)
+/- baricitinib	JAK inhibitor may blunt inflammatory responses	• Remdesivir plus baricitinib may improve outcomes
Dexamethasone	Steroid – blunts inflammatory response after acute phase of infection	• Hospitalized patients • Reduced death from 41.4% to 29.3% (ventilator) • Reduced death from 26.2% to 23.3% (supplemental O2) • No effect (possible increase) in patients not on respiratory support

Veklury™ prescribing information, 10/2020; RECOVERY trial, NEJM 2020

COVID-19 treatments: antibodies

Drug	Mechanism of action	Clinical use
Bamlanivimab (Lilly/AbCellera)	Neutralizes/clears virus	• Age 12 or over, non-hospitalized, high risk for severe disease, within 10 days of symptom onset • Reduced hospitalization/ER visits from 10% to 3%
Casirivimab/ Imdevimab (Regeneron)	Neutralizes/clears virus	• Age 12 or over, non-hospitalized, high risk • Reduced hospitalization/ER visits from 9% to 3%
Convalescent plasma	Neutralizes/clears virus (COVID-19 antibody dose varies by plasma donor)	• Hospitalized patients • Reduced death in non-intubated patients 49.4% to 41.5%, particularly in those ≤80yrs (46.6% > 33.2%)

https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs

COVID-19 vaccines

Manufacturer	Vaccine type	Clinical use
Pfizer/BioNTech (EUA 11/20/20)	mRNA nanoparticle	• 95% effective at preventing infection at 4 weeks • No serious safety concerns reported to date
Moderna (EUA 11/30/20)	mRNA nanoparticle	• 94.1% effective, symptomatic infection at 6 weeks • No serious safety concerns reported to date
AstraZeneca/ Oxford	Adenovirus	• 70% effective at preventing infection (62-90%) • Data collection and analysis ongoing
Janssen, Novavax, intl pharma	Adenovirus Protein nanoparticle	• Phase 3 trials ongoing

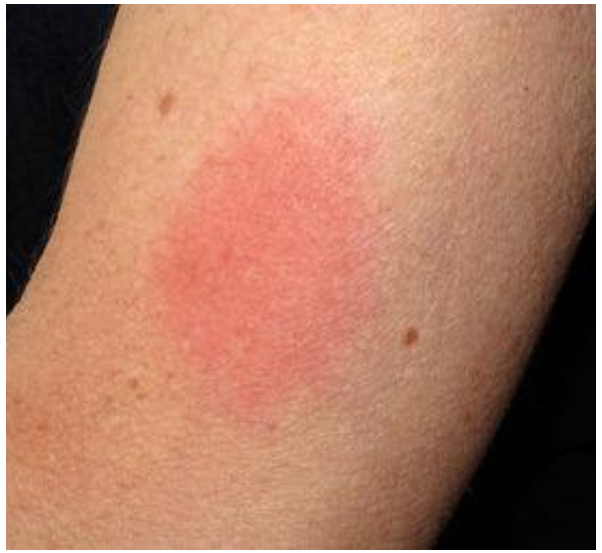
None of these are “live” vaccines

Immunosuppressed patients were excluded from Pfizer/Moderna/AstraZeneca vaccine trials

Company website information

COVID-19 vaccines: expected side effects

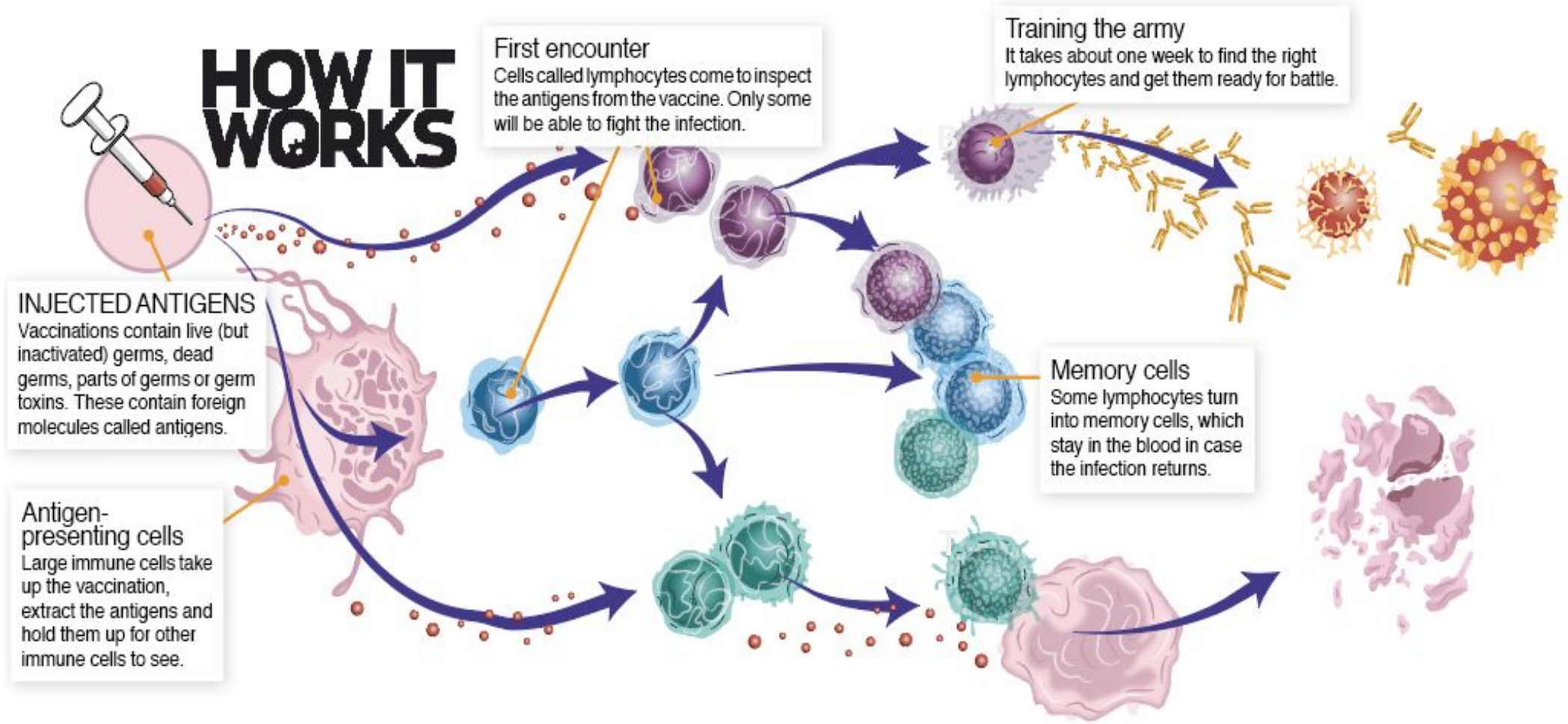
Side effect	Frequency
Fever > 39C (102.2F)	2%
Fatigue	4% (Pfizer) – 10% (Moderna)
Muscle aches	9%
Joint pain	5%
Headache	2% (Pfizer) – 5% (Moderna)
Pain/redness at injection site	2-4%



Redness at injection site from shingles vaccine

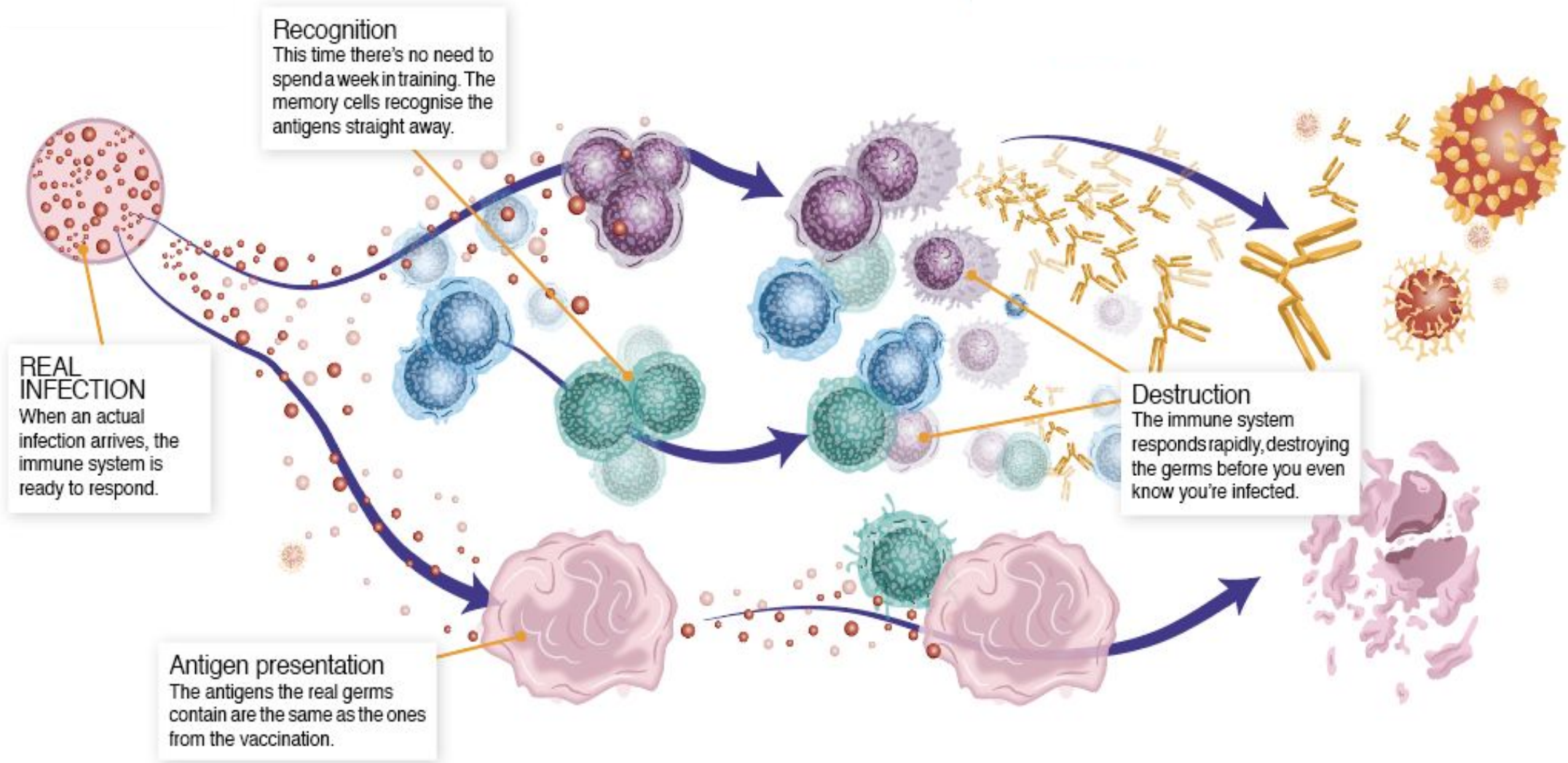
https://www.sciencemag.org/news/2020/11/fever-aches-pfizer-moderna-jabs-aren-t-dangerous-may-be-intense-some

How vaccines work (part 1)



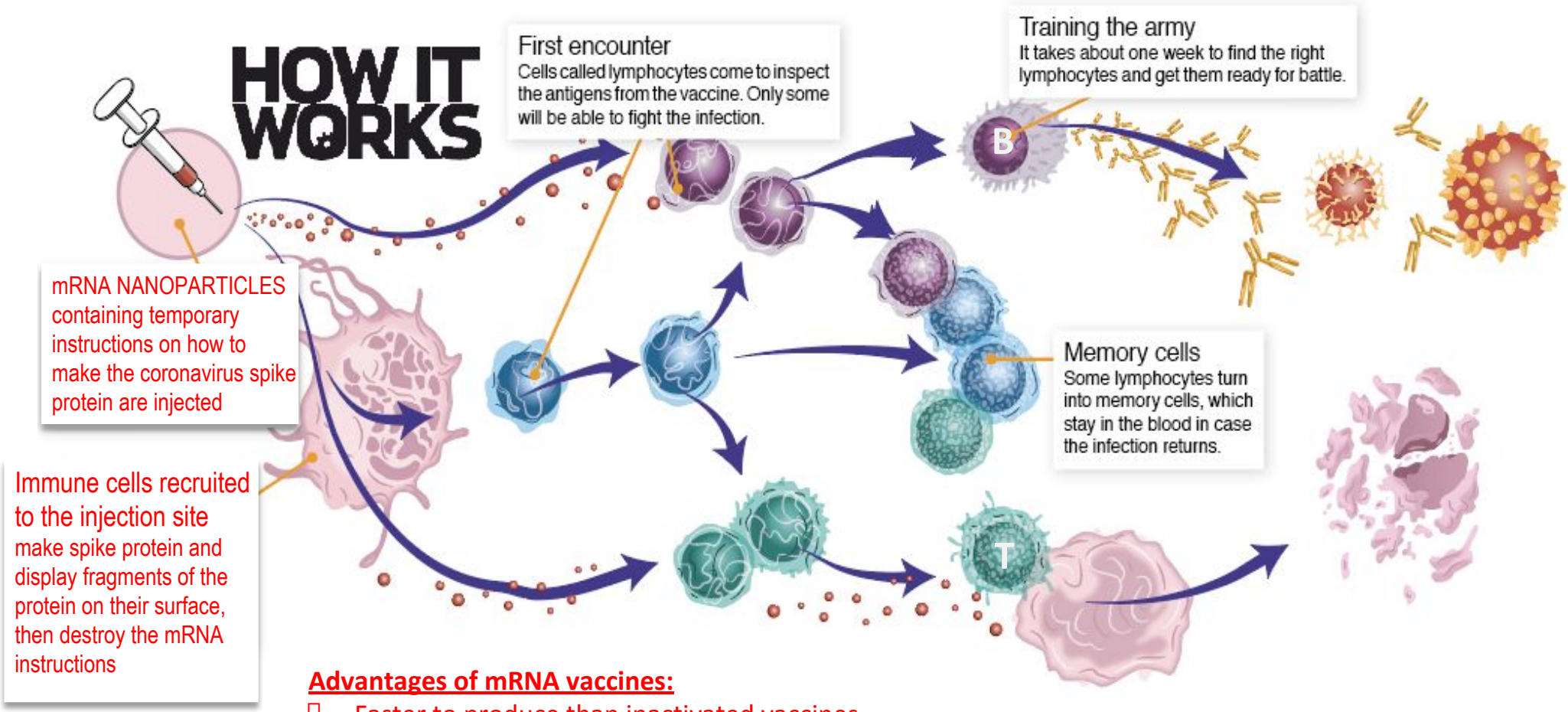
https://www.howitworksdaily.com/the-human-body-how-vaccines-work/

How vaccines work (part 2)



https://www.howitworksdaily.com/the-human-body-how-vaccines-work/

mRNA versus inactivated vaccines



Advantages of mRNA vaccines:

- Faster to produce than inactivated vaccines (could theoretically adapt mid-season if the virus mutates)
- Potentially broader and more effective antigen presentation

https://www.howitworksdaily.com/the-human-body-how-vaccines-work/

COVID-19 vaccines and P/P medications

Drug	Expected effect	Potential actions
Prednisone MTX/AZA/MMF	Reduced efficacy (relative to dose)	Immunize while on medications
Dapsone	uncertain	Immunize while on medications
Doxycycline	minimal	Immunize while on medications
IVIG	May reduce (time-dependent)	Efficacy may be reduced if vaccine is administered less than 2 weeks before or up to 2-8 mos after IVIG
Rituximab	May reduce (time- and dose-dependent)	Efficacy will be reduced (complete vaccination at least 2-4wks before or 4-6 months after rituximab). 12 months after RTX considered within normal range.

IMPORTANT NOTE: Formal recommendations await FDA recommendations after review of EUA requests!

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4462293/#__sec11title
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5042271/

COVID-19 vaccines

VACCINE	VACCINE EFFECTIVENESS	# OF RECOMMENDED DOSES
Flu (Influenza)	44.0% - 60%	1
AstraZeneca novel coronavirus	70.0%	2
Chickenpox (Varicella)	92.0%	2
Moderna novel coronavirus	94.1%	2
Pfizer novel coronavirus	95.0%	2
Measles (MMR)	97.0%	2
Polio	99.0%	3–4

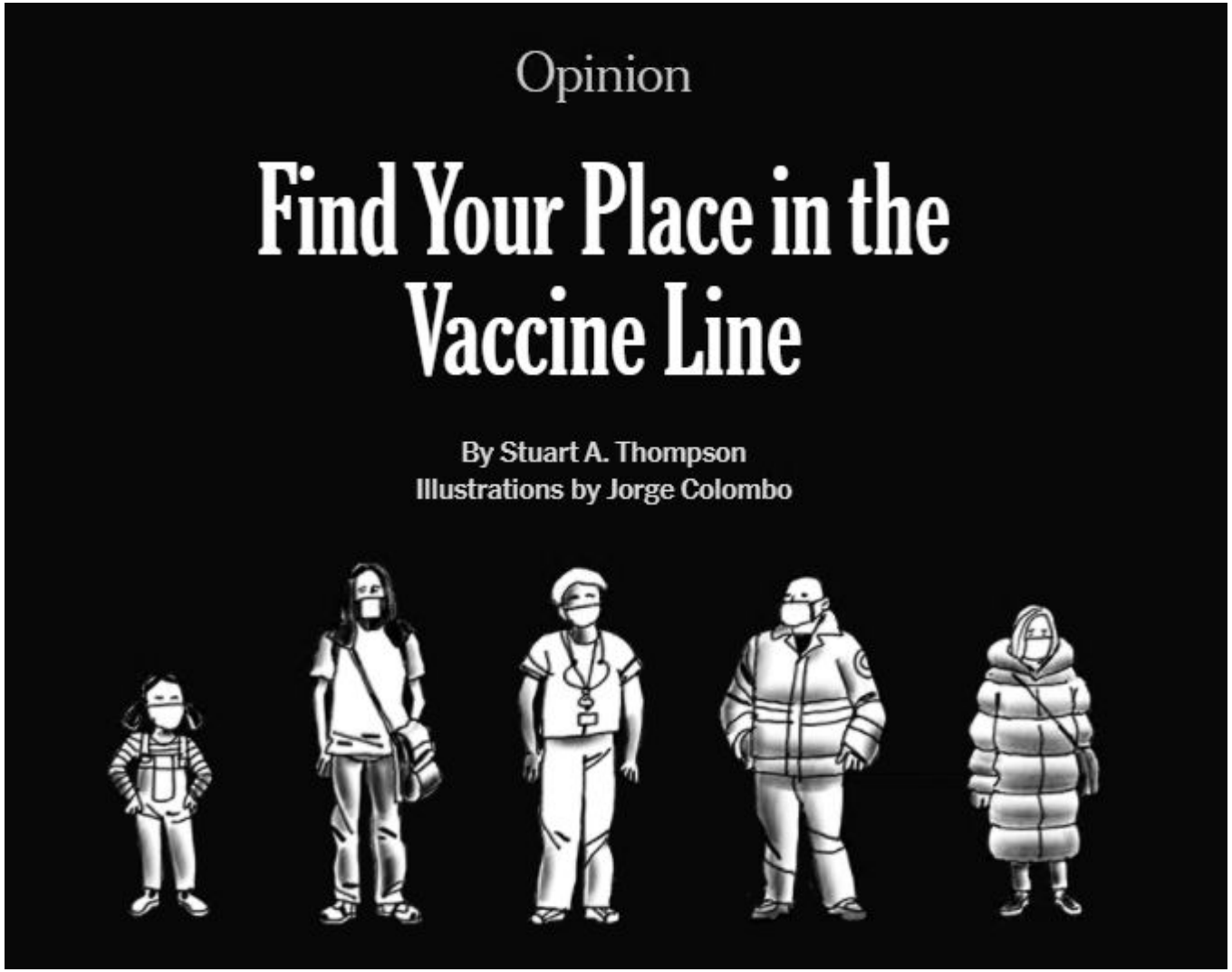
https://www.businessinsider.com/how-pfizer-coronavirus-vaccine-compares-other-vaccines-2020-11

COVID-19 vaccine distribution

Approximately 70M doses of vaccine are expected to be available by end of 2020
Masks and social distancing will likely be recommended at least through summer 2021 (potentially longer)

https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2020-12/COVID-02-Dooling.pdf

COVID-19 vaccine distribution



How old are you?

What county do you live in?

Do you work in these professions?

- ○ Health care worker
- ○ Essential worker
- ○ First responder
- ○ Teacher
- ◉ None of these

If an essential worker, you've probably been working in person throughout the pandemic in a vital industry like health, food or energy.

Do you have Covid-related health risks?

- ○ Yes
- ◉ No

These include conditions tied to increased risk of Covid death, like heart disease, cancer, diabetes, obesity or other immunocompromised conditions.

SUBMIT

https://www.nytimes.com/interactive/2020/12/03/opinion/covid-19-vaccine-timeline.html

Thanks for your attention!
Q&A