Disclosure

• Neither I nor any member of my immediate family has a financial relationship or interest (currently or within the past 24 months) with any proprietary entity producing health care goods or services consumed by, or used on, patients related to the content of this CME activity.

• I do not intend to discuss an unapproved/investigative use of a commercial product/device.
Objectives of talk

- History of COVID
- Pandemic playbooks and school closures
- COVID vaccines including child vaccines
- COVID variants/Omicron
- What defines endemicity?
- Masks
How do new infectious diseases “emerge” or enter human populations?

<table>
<thead>
<tr>
<th>Activity</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global Warming</strong></td>
<td>• Pathogens can go to new niches, have access to new hosts</td>
</tr>
<tr>
<td><strong>Interaction with animals (hunting, eating, pets)</strong></td>
<td>• Zoonoses is when a microbe jumps from nonhuman to human hosts</td>
</tr>
<tr>
<td><strong>Changes in agriculture</strong></td>
<td>New crops attract new pests</td>
</tr>
<tr>
<td><strong>Encroachment on animal habitats</strong></td>
<td>• Other animals crowded, microbes can mutate, mix</td>
</tr>
<tr>
<td></td>
<td>• Destruction of rain forests bring humans into contact with unfamiliar microbes</td>
</tr>
<tr>
<td><strong>Urbanization</strong></td>
<td>• People more crowded together, contagious diseases</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>• Jet travel spreads diseases even when asymptomatic</td>
</tr>
<tr>
<td></td>
<td>• Ships can carry “unintended passengers”</td>
</tr>
<tr>
<td></td>
<td>• Breakdown of public health measures, poverty, war, famine, intent to harm</td>
</tr>
</tbody>
</table>
In 2002, there was another virus (identified in China) called “SARS” - Severe Acute Respiratory Syndrome (SARS-CoV-1).

SARS lasted about 9 months in the world until 2003; 8098 cases, 29 countries, 774 deaths.

- 29 cases in U.S. but 0 deaths, more in Canada
- Horseshoe bat, then cat-like mammal called palm civet → human → human to human
Middle East respiratory syndrome coronavirus in 2012 (MERS-CoV)

- First came out in Saudi Arabia in 2012; all cases linked to Middle East
- Went around world from 2012-2019: 27 countries, 2494 cases, 858 deaths
- United States: 2 cases in May 2014 (Indiana, Florida) – both health care workers from Saudi Arabia
- Was originally in camel and then went to humans then human to human
SARS-CoV-2 history

• Illness with fever, cough, pneumonia reported from Wuhan, China on New Years’ Eve to WHO (December 31, 2019)
• January 7, 2020: Identified etiology a new coronavirus
• Has been spreading around world since then
• January 30, 2020: WHO - “global health emergency”
• March 11, 2020: WHO – “Pandemic”
• March 26, 2020 – US becomes epicenter of pandemic (not for first time)
• December 11, 2020: First EUA from FDA for COVID-19 vaccine in US (Pfizer)
• 6.15 million deaths
HIV and COVID-19, something to do with animal treatment

Jane Goodall: COVID-19 is a product of our unhealthy relationship with animals and the environment (commentary)
CHILDREN AND COVID AND PANDEMIC PLAYBOOKS
Children much less at risk for severe disease than adults

Deaths in children and young people in England after SARS-CoV-2 infection during the first pandemic year

• From March 2020-February 2021, ~12 million children <18 in England
• 3105 died during this time of all causes, 25 from SARS-CoV-2 (0.8%): 22 due to COVID & 3 due to pediatric MISC
• 99.995% of children 18 with a positive COVID test survived
• In contrast, 99% adults before vaccines survived but that is high mortality rate (100K deaths in England among adults during same period)
In US

Widespread vaccination of adults helps protect unvaccinated children.

• Also <0.1% deaths in children from COVID in US <18
• CDC from coding error had overestimated but just removed 25% of pediatric deaths from tracker
• Delta surge in US - we had fewer unvaccinated adults than UK
• Vaccinated adults protect kids

<table>
<thead>
<tr>
<th>Age Group</th>
<th>COVID-19 Deaths</th>
<th>Total Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Ages</td>
<td>983,409</td>
<td>7,638,997</td>
</tr>
<tr>
<td>Under 1 year</td>
<td>248</td>
<td>42,516</td>
</tr>
<tr>
<td>0-17 years</td>
<td>962</td>
<td>75,444</td>
</tr>
<tr>
<td>1-4 years</td>
<td>121</td>
<td>7,931</td>
</tr>
<tr>
<td>5-14 years</td>
<td>303</td>
<td>12,627</td>
</tr>
<tr>
<td>15-24 years</td>
<td>2,592</td>
<td>81,010</td>
</tr>
<tr>
<td>18-29 years</td>
<td>6,129</td>
<td>143,041</td>
</tr>
<tr>
<td>25-34 years</td>
<td>10,936</td>
<td>171,262</td>
</tr>
<tr>
<td>30-39 years</td>
<td>17,807</td>
<td>212,192</td>
</tr>
<tr>
<td>35-44 years</td>
<td>27,244</td>
<td>253,771</td>
</tr>
<tr>
<td>40-49 years</td>
<td>42,366</td>
<td>318,113</td>
</tr>
<tr>
<td>45-54 years</td>
<td>65,639</td>
<td>450,584</td>
</tr>
<tr>
<td>50-64 years</td>
<td>184,388</td>
<td>1,291,294</td>
</tr>
<tr>
<td>55-64 years</td>
<td>144,569</td>
<td>1,020,383</td>
</tr>
<tr>
<td>65-74 years</td>
<td>226,178</td>
<td>1,563,066</td>
</tr>
<tr>
<td>75-84 years</td>
<td>253,601</td>
<td>1,852,728</td>
</tr>
<tr>
<td>85 years and o</td>
<td>251,978</td>
<td>2,183,119</td>
</tr>
</tbody>
</table>


BMJ 2022; 376: doi: https://doi.org/10.1136/bmj.o831 (Published 29 March 2022)
Cite this as: BMJ 2022;376:o831
Ages 0-17 = 0.1% of COVID deaths (23% pop) in CA
Potential mechanism: lower expression of ACE-2 receptors?

Figure. Nasal Gene Expression of ACE2 in Different Age Groups
Innate immunity might be the key to why children have fared better with the virus.

By contrast, the children in the study had higher levels of the signalling proteins interferon-γ and interleukin-17, which alert the immune system to the arrival of a pathogen. These were probably produced by cells that line the airways, and are involved in mediating innate immunity. Herold suspected that innate immune system seems to help children with COVID-19 (72% of children who died of COVID-19 had immune defects or other medical conditions).
MEASLES AND SCHOOL CLOSURE.

MEASLES is rife just now in many parts of the country, as at Motherwell in Scotland and Tipton in Staffordshire. The absentees from school at the former place number 27 per cent. of the scholars, at the latter about 50 per cent. In face of this, the question of closing the schools at Dalziel has been adjourned for a week by the Motherwell authorities; whilst at Tipton nothing has been done beyond characterising the report of the school attendance officer as "exaggerated." School authorities seem to be still slow to learn that it is the wisest plan to allow their schools to be closed in the early beginnings of an epidemic, before widespread prevalence has rendered their tardy acquiescence in closure a futile and nugatory step.
ID pandemics and school closures-
Influenza doesn’t differentially spare younger children
In 1918 influenza pandemic, schools closed for 4 months at most.
At Height of the 1918 Pandemic, NYC and Chicago Schools Stayed Open. Here's Why

Amid fierce controversy, public health officials in both cities decided children would be better off in classrooms.
By 1918, high public school attendance and mandatory attendance laws in each state; schools were place for food, learning and safety

As the second wave of the Spanish flu hit in September 1918, Dr. Royal S. Copeland, a homeopathic physician and the city's health commissioner, initially considered school closures as a way of limiting the pandemic's spread. But Dr. S. Josephine Baker, director of the Department of Health Bureau of Child Hygiene and a leading Progressive reformer, persuaded Copeland to keep the city's schools open, according to a 2010 article co-authored by Dr. Alexandra Stern. Baker argued that kids were better off contained in schools, and that regular medical inspections could identify sick students and keep healthy ones safe.

At the time, New York City's public school system contained close to 1 million children, and 750,000 of those lived in crowded and often unsanitary tenement homes. In an article headlines “Epidemic Lessons Against Next Time," published in the New York Times in November 1918, after the worst of the pandemic had passed, Copeland described the advantages in keeping the schools open: “[Children] leave their often unsanitary homes for large, clean, airy school buildings, where there is always a system of inspection and examination enforced,” he said.
“Better Off in School”: School Medical Inspection as a Public Health Strategy During the 1918–1919 Influenza Pandemic in the United States

SYNOPSIS

During the 1918–1919 influenza pandemic in the United States, most cities responded by implementing community mitigation strategies, such as school closure. However, three cities—New York City, Chicago, and New Haven, Connecticut—diverged from the dominant pattern by keeping their public schools open while the pandemic raged. This article situates the experiences of these three cities in the broader context of the Progressive era, when officials and experts put great faith in expanding public programs in health and education. It adds an important dimension to the historical understanding of the
Ontario schools practiced blowing noses but stayed open
Other cities (like Berkeley) closed schools but for 4 months at most as no other option; others held school outside
Schools re-opened in US in 1918 with following:

- Sometimes masks, not universally
- Outside work
- Wide open windows for ventilation
- School nurses
- Stay home when sick
- Wash hands
- School lunch programs
FIGURE 2
School closure status in number of days and by region, from March 2020 to February 2021 (weighted average)

Source: UNESCO Global monitoring of school closures caused by COVID-19
Despite overwhelming evidence of the impact of school closures on children, and despite increasing evidence that schools are not drivers of the pandemic, too many countries have opted to keep schools closed, some for nearly a year.

Schools are essential for children’s learning, health, safety and well-being. For the most vulnerable children, school closures have deprived them of their one nutritious meal a day; children living in violent or dysfunctional family settings who rely on school to provide a safe, nurturing environment have also been cut off from this safety net (Borkowski et al, 2020; WHO, 2020). In many countries, schools also play essential role in immunization and health support.
Mixed re-opening in the United States 2020-2021 School Year

Average In-Person Index By State (excluding DC)

Source: https://cai.burbio.com/school-opening-tracker/
## Fall 2020: Transmission in school settings vs community

<table>
<thead>
<tr>
<th>Setting</th>
<th>Time Period</th>
<th># Students/Staff</th>
<th>Community Spread (per 100K/week)</th>
<th>Masks</th>
<th>Distance</th>
<th>Ventilation</th>
<th>Other</th>
<th>In School Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chicago Parochial Schools</td>
<td>Aug - Oct 2020</td>
<td>19,600/2,750</td>
<td>85 - 93 cases</td>
<td>Yes</td>
<td>6 ft</td>
<td>Not described</td>
<td>Handwashing, Symptom screening &amp; Temp checks</td>
<td>3 clusters (2 staff -&gt; staff, 1 staff -&gt; student)</td>
</tr>
<tr>
<td>North Carolina Public Schools</td>
<td>Aug - Oct 2020</td>
<td>~100,000</td>
<td>100 - 200 cases</td>
<td>Yes</td>
<td>6 ft</td>
<td>No</td>
<td>Handwashing, Symptom screening &amp; Temp checks</td>
<td>32 cases (no student -&gt; staff)</td>
</tr>
<tr>
<td>NYC Public Schools</td>
<td>Oct - Nov 2020</td>
<td>~288,000/80,000</td>
<td>89 - 297 cases</td>
<td>Yes</td>
<td>6 ft</td>
<td>Open windows/ upgrades where Hybrid Surveillance testing</td>
<td>0.6% secondary attack rate (staff index 78% of cases)</td>
<td></td>
</tr>
<tr>
<td>Wisconsin Public Schools</td>
<td>Sep - Nov 2020</td>
<td>4,876/654</td>
<td>~420 cases</td>
<td>Yes</td>
<td>6 ft</td>
<td>Not described</td>
<td>Cohorting</td>
<td>7 cases</td>
</tr>
<tr>
<td>Georgia Public Schools</td>
<td>Dec 2020 - Jan 2021</td>
<td>2,600/700</td>
<td>194 - 704 cases</td>
<td>Yes</td>
<td>&lt;6 ft + plexiglass</td>
<td>Not described</td>
<td>Cohorting</td>
<td>9 clusters of ≥3 cases (13 staff/32 students)</td>
</tr>
<tr>
<td>Utah Public Schools</td>
<td>Dec 2020 - Jan 2021</td>
<td>10,171/1,214</td>
<td>290 - 670 cases</td>
<td>Yes (95%)</td>
<td>3 ft</td>
<td>Open doors/ windows (80%) Air Filtration Enhanced hand hygiene/disinfection</td>
<td>5 cases (secondary attack rate 0.7%)</td>
<td></td>
</tr>
</tbody>
</table>


Slide courtesy of Lillian Brown MD, PhD
Schools not major source of infection for youth

- Cases in schools highly correlated to case rates in the community\textsuperscript{1,2}

- Close contact with a known case, social gatherings most likely to be associated with infection in school age children\textsuperscript{2}

- Activities associated with youth sports emerged as source of outbreaks/transmission\textsuperscript{3,4}

\textsuperscript{1}Doyle et al, MMWR 2021; \textsuperscript{2}Hobbs et al, MMWR 2021; \textsuperscript{3}Siegel et al, MMWR 2021; \textsuperscript{4}Minnesota Department of Public Health

\textsuperscript{4}Sports includes 30 high school teams, 10 club teams, 12 teams in a sports association, and three fitness/rec centers.
PROTECTING YOUTH MENTAL HEALTH

The U.S. Surgeon General's Advisory

December 2021

AAP, AACAP, CHA declare national emergency in children's mental health

October 19, 2021
Large test-to-stay program in MA winter 21-22

"In-school transmission extremely rare" as Mass. starts new COVID-19 at home tests for students, teachers

1/18/2022

- Large test to stay program launched fall-winter 2021
- As of Jan. 9, 2002: 503,312 Test and Stay tests had been conducted; 496,440 of them were negative (almost 99%)
- Formed basis of Policy Lab recommendation CHOP on testing
School quarantines keep too many kids at home — with barely any effect on covid

Some states and school districts are shifting — against the CDC's advice — to a sensible 'test and stay' approach.

By Jeffrey Vergales and Monica Gandhi

October 5, 2021 at 6:00 a.m. EDT
Lessons from the History of Quarantine, from Plague to Influenza A

Eugenia Tognotti

surveillance proved effective in containing the global threat in just over 3 months. For centuries, these practices have been the cornerstone of organized responses to infectious disease outbreaks. However, the use of quarantine and other measures for controlling epidemic diseases has always been controversial because such strategies raise political, ethical, and socioeconomic issues and require a careful balance between public interest and individual rights. In a globalized world that is becoming ever more vulnerable to communicable diseases, a historical perspective can help clarify the use and implications of a still-valid public health strategy.
Roadmap – Policy Lab
Children’s Hospital of Pennsylvania

• **Vaccinate:** Down to 5 now but 6 months-6 years coming (Moderna 25 micrograms x 2)

• **Masks:** Mask mandates for all release on hospitalization metrics in community (e.g. <10/100K COVID hospitalizations)- CDC did this on February 24, 2022

• **Testing:** No more asymptomatic testing in schools per Policy Lab, CHOP

• **Symptoms:** Symptom based management, stay home when sick

• **Ventilation**

• **No quarantines (wear mask if exposed)**

• School nurses

• Restore joy to school
There are actually 8 unique vaccines approved by WHO for COVID-19 (Sputnik V pending), three authorized in U.S.

<table>
<thead>
<tr>
<th>Company or name</th>
<th>Type of vaccine</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderna</td>
<td>mRNA vaccine</td>
<td>Baden NEJM, Feb 4, 2021</td>
</tr>
<tr>
<td>Pfizer</td>
<td>mRNA vaccine</td>
<td>Polack NEJM, December 31, 2020</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>Adenovirus + DNA vaccine</td>
<td>Voysey Lancet December 8, 2020; Preprint Feb 1, 2021</td>
</tr>
<tr>
<td>Novavax</td>
<td>Spike protein + an adjuvant</td>
<td>Novavax press release June 14; Novavax NEJM June 30, 2021</td>
</tr>
<tr>
<td>Sputnik V</td>
<td>Adenovirus + DNA vaccine</td>
<td>Logunov Lancet, February 2, 2021</td>
</tr>
<tr>
<td>SINOPHARM</td>
<td>Whole inactivated virion</td>
<td>Sinopharm, JAMA, May 28, 2021</td>
</tr>
<tr>
<td>Sinovac</td>
<td>Whole inactivated virion</td>
<td>Sinovac, JAMA May 28, 2021</td>
</tr>
<tr>
<td>Bharat</td>
<td>Whole inactivated virion</td>
<td>Bharat Covaxin, April 21, 2021</td>
</tr>
</tbody>
</table>
6 vaccine candidates to date involve spike protein and receptor binding domain of SARS-CoV-2 — either mRNA or adenoviral-vector DNA vaccines or protein adjuvant itself; 3 inactivated virus
Three types of vaccines involving spike protein

- mRNA vaccines (2)
- Adenoviral vector DNA vaccines (3)
- Spike protein + M-adjuvant vaccine (1)

Three vaccines whole inactivated virions
Remember immunity - antibodies and cell-mediated memory T cells and memory B cells produce antibodies. Remember, antibodies will wane with time, but memory B cells are the blueprint to make more.

Most vaccine trials measured antibodies and T cell responses. CD4+ T cells are Th1 cells for intracellular pathogens, and Th2 cells for extracellular pathogens. CD8+ T cells are cytotoxic T cells. Cytotoxic T cells are the major immune defense against viruses and are preserved.

Of note, want Th1:Th2 ratio >>1 for viruses; Th2 CD4s block antiviral Th1-CD4s and CD8s.
<table>
<thead>
<tr>
<th>Company</th>
<th>Platform</th>
<th>Doses</th>
<th>Non-clinical results</th>
<th># with vaccine (same placebo)</th>
<th>Protection from COVID-19 hospitalization</th>
<th>Protection from COVID severe dz (some at home)</th>
<th>Efficacy against milder COVID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderna</td>
<td>mRNA-1273 mRNA in lipid nanoparticle</td>
<td>2</td>
<td>Neutralizing Abs; Strong Th1 CD4+ protection from challenge (macaques)</td>
<td>~15,000</td>
<td>90% (1 in vaccine arm after 2nd dose hospitalized)</td>
<td>97% (30 cases in placebo arm; 0 in vaccine reported but 1 severe per FDA)</td>
<td>94.1%</td>
</tr>
<tr>
<td>Pfizer</td>
<td>BNT162b2 mRNA in lipid nanoparticle</td>
<td>2</td>
<td>Neutralizing Abs; Strong Th1 CD4+, CD8+; protection from challenge (macaques)</td>
<td>~18,600</td>
<td>100%</td>
<td>100% (9 cases in placebo arm; 0 in vaccine- initially severe but not)</td>
<td>95%</td>
</tr>
<tr>
<td>Johnson &amp; Johnson</td>
<td>JNJ-78436725 Non-replicating human adenovirus/DNA</td>
<td>1</td>
<td>Neutralizing Abs; Strong Th1 CD4+ &gt; Th2; CD8+; challenge protection (macaque)</td>
<td>~22,000 US, Latin America, S. Africa</td>
<td>100%</td>
<td>85.4% across 3 sites (7 deaths, 16 hospitalizations, all in placebo arm)</td>
<td>72% US; 61% Latin America; 64% S. Africa (95% B1.351)</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>AZD 1222 Non-replicating Chimp Adenovirus-DNA</td>
<td>2</td>
<td>Neutralizing Abs; Strong Th1 CD4+ &gt; Th2; CD8+; protection from challenge (macaques)</td>
<td>~28,588 (UK, SA, US/Peru/Chili)</td>
<td>100%</td>
<td>100% (UK, 15 placebo arm hospitalized, 0 in vaccine; US, 8 severe in placebo, 0 vaccine)</td>
<td>76% US (85% in &gt;65 yrs); 70% UK; S. Africa halted for mild</td>
</tr>
<tr>
<td>Novavax</td>
<td>NVX-CoV2373 Spike protein/RBD + Matrix M adjuvant</td>
<td>2</td>
<td>Neutralizing Abs; Strong Th1 CD4 &gt; Th2; macaque challenge protection</td>
<td>8833 (Phase 3 UK; 2b SA); 12.5K (Φ 3)</td>
<td>100%</td>
<td>100% (24 severe placebo in UK/SA/US/MX; 0 vaccine)</td>
<td>90.4% US/MX; 100% severe; 93.2% variants</td>
</tr>
<tr>
<td>Sputnik V</td>
<td>Ad26 and Ad5 adenovirus/DNA</td>
<td>2</td>
<td>NAbs; IFN-γ secretion PMBCs, cellular response</td>
<td>~14964</td>
<td>100%</td>
<td>100% (20 in placebo; 0 vaccine)</td>
<td>91.6%</td>
</tr>
<tr>
<td>Company</td>
<td>Platform</td>
<td>Doses</td>
<td>Non-clinical results</td>
<td># with vaccine (same placebo)</td>
<td>Protection from COVID-19 hospitalization</td>
<td>Efficacy against milder COVID</td>
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<td></td>
</tr>
<tr>
<td>BHARAT</td>
<td>Inactivated whole virus</td>
<td>2</td>
<td>Neutralizing Abs; Strong Th1 CD4 responses in phase II trial (<a href="#">Lancet</a>)</td>
<td>11,000 (<a href="#">press release</a> 4/21)</td>
<td>100%</td>
<td>78%</td>
<td></td>
</tr>
<tr>
<td>SINOVAC</td>
<td>Whole inactivated virion</td>
<td>2</td>
<td>Neutralizing Abs; IFN-gamma assays T cell responses</td>
<td>13,068</td>
<td>100%</td>
<td>72.8%</td>
<td></td>
</tr>
<tr>
<td>SINOPHARM</td>
<td>Whole inactivated virion</td>
<td>2</td>
<td>Neutralizing Abs; IFN-gamma assays T cell responses</td>
<td>13,068</td>
<td>100%</td>
<td>78.1%</td>
<td></td>
</tr>
</tbody>
</table>
T cells work against variants

Broad T cell repertoire (100s of T cells across spike protein) after infection. Means viral escape of T cell-immunity (from both natural infection and vaccination) unlikely, re-infection if happens mild.
Then look at T-cell response to variants after vaccines - still intact - and expand with every exposure

Negligible impact of SARS-CoV-2 variants on CD4+ and CD8+ T cell reactivity in COVID-19 exposed donors and vaccinees.


- T cell reactivity against variants remain intact if you had natural infection or mRNA vaccination from alpha to Omicron.
Data from NY during delta shows that vaccine effectiveness AGAINST SEVERE DISEASE not waning except for older individuals

https://www.medrxiv.org/content/10.1101/2021.10.08.21264595v1.full.pdf
Memory B cells from vax or infection adapt to whatever variant they see; T cells cover any variant.
<table>
<thead>
<tr>
<th>Country/region</th>
<th>Scientific name</th>
<th>WHO name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kent, UK</td>
<td>B.1.1.7</td>
<td>Alpha</td>
</tr>
<tr>
<td>South Africa</td>
<td>B.1.351</td>
<td>Beta</td>
</tr>
<tr>
<td>Brazil</td>
<td>P.1</td>
<td>Gamma</td>
</tr>
<tr>
<td>India</td>
<td>B.1.617.2</td>
<td>Delta</td>
</tr>
</tbody>
</table>
Omicron’s feeble attack on the lungs could make it less dangerous

Mounting evidence from animal studies suggests that Omicron does not multiply readily in lung tissue, which can be badly damaged in people infected with other variants.

- More and more immunity in the population – 60-75% of the world’s population may be exposed to Omicron
- On top of an 80% seroprevalence in adults in S. Africa for instance (70% in children by NIH study in US)
- A less virulent influenza variant in 1918? (3rd wave)
- If you see Omicron, you get immunity across whole virus
- If not, a booster will help; older patients should get booster if infected prior- hybrid immunity
- In the future we may need whole inactivated virus vaccine as a booster (Covaxin, etc.)- to get immunity across whole virus to combat variants
Whom did 1st booster benefit? And 4th shots?

- Data from CDC (February 18), Israel, and UK converged on the fact that boosters most benefitted those over 65 & some benefit over 50 (4/million deaths vs 1/million deaths)
- NEJM study December 23, 2021 showed no COVID-19 deaths in those 18-29 with two doses of the vaccine (0 deaths in 3 vs 2 doses)
- NEJM study looked at 4th shot in health care workers & found no benefit <60
- European CDC approved for >80; White House encouraging for >60

**44x Higher in Unvaccinated Adults Ages 18 Years and Older**

- 30x Higher in Unvaccinated Adults Ages 18-49 years
- 45x Higher in Unvaccinated Adults Ages 50-64 years
- 51x Higher in Unvaccinated Adults Ages 65 Years and Older
Age-Adjusted Rates of COVID-19-Associated Hospitalizations by Vaccination Status in Adults Ages ≥18 Years, January 2021–January 2022

During Omicron surge
After 2-dose vaccination


- Even with 2 doses, risk of COVID-19 death 0.00003 after vaccination
- Risk factors for severe breakthrough (4th dose): severe immunocompromise, >75 with 4 comorbidities
- Explains who needs likely 4th booster; Paxlovid nearby
Extending dosing interval increases T cell & antibodies

Immunologic research shows better antibody response and importantly CD4 T cell responses if extend interval on Pfizer vaccine to 6-8 weeks instead of 3 weeks; October 15, 2021.
Data from Canada shows Pfizer works better if extend interval to 7-8 weeks (both against infection and severe disease) - associated with more safety (myocarditis)
CDC has only advertised interval to professionals, not public or media 2/22/22

**Extend the Interval Between COVID Vaccine Doses**

— The safety and effectiveness data should prompt CDC to update its policy

by Michael Daignault, MD, and Monica Gandhi, MD, MPH  February 14, 2022

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**TABLE 2. COVID-19 vaccination schedule for the primary series in the general population***

<table>
<thead>
<tr>
<th>Primary series vaccine manufacturer</th>
<th>Age group</th>
<th>Number of doses in primary series</th>
<th>Number of booster doses</th>
<th>Interval between 1st and 2nd dose</th>
<th>Interval between primary series and booster dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer-BioNTech</td>
<td>5-11 years</td>
<td>2</td>
<td>NA</td>
<td>3 weeks</td>
<td>NA</td>
</tr>
<tr>
<td>Pfizer-BioNTech</td>
<td>≥12 years</td>
<td>2</td>
<td>1</td>
<td>3-8 weeks’</td>
<td>≥5 months</td>
</tr>
<tr>
<td>Moderna</td>
<td>≥18 years</td>
<td>2</td>
<td>1</td>
<td>4-8 weeks’</td>
<td>≥5 months</td>
</tr>
<tr>
<td>Janssen</td>
<td>≥18 years</td>
<td>1</td>
<td>1</td>
<td>NA</td>
<td>≥2 months</td>
</tr>
</tbody>
</table>

*For the vaccination schedule for people who are moderately or severely immunocompromised, see Table 3

*An 8-week interval may be optimal for some people ages 12 years and older, especially for males ages 12 to 39 years. A shorter interval (3 weeks for Pfizer-BioNTech; 4 weeks for Moderna) between the first and second doses remains the recommended interval for: people who are moderately to severely immunocompromised; adults ages 65 years and older; and others who need rapid protection due to increased concern about community transmission or risk of severe disease.
Omicron created a lot of natural immunity

60% of adults and 75% of children 0-18 in the US have had exposure to COVID-19
Omicron seemed to show power of “hybrid immunity”
Omicron reduced protection from either former infection or vaccines for mild (not severe) disease

- Qatar study showed that protection from re-infection after infection declined from ~90% with the Alpha, Beta and Delta variants to 56% against Omicron
- Canada study showed protection after two-dose vaccination declined from 89% against Delta to 36% against Omicron.
- Omicron variant to evade antibodies, although the protection against severe disease due to cellular immunity from either vaccination or infection is more durable.
- A study among employees at the Cleveland Clinic verifies that one booster dose of the vaccine after either two-dose vaccination or natural infection protects against subsequent re-infection with Omicron.
- Single dose of the Pfizer COVID-19 vaccine after recovery protected against re-infection during the Delta surge by at least 3-fold, with two doses conferring no additional benefit.
- Recovery immunity waned after a year but was higher than 90% in those with subsequent vaccination.
Daily new confirmed COVID-19 deaths per million people
7-day rolling average. Due to varying protocols and challenges in the attribution of the cause of death, the number of confirmed deaths may not accurately represent the true number of deaths caused by COVID-19.

Deaths at lowest point in pandemic worldwide since beginning of pandemic
WHO Lays Out Plan to Emerge From Emergency Phase of Pandemic

By Julie Steenhuisen and Mrinalika Roy
March 31, 2022

March 30, 2022- Excess mortality from other medical conditions not being worked on – so this is plan for COVID

Base scenario

Best case: Less virulent variant emerges

Vaccinate vulnerable groups every winter

Most won’t need re-vaccination

Worst case: More virulent variant emerges

Boost everyone & consider whole virus vaccine
ENDEMICITY
COVID-19 likely to be controlled not eradicated – so frequency of boosters will depend on variants

- **Control:** Reduction of disease incidence to acceptable levels
- **Elimination:** Reduction to zero incidence in a defined geographical area
- **Eradication:** Permanent reduction to zero worldwide
- **Extinction:** Infectious agent no longer exists in nature or laboratories.
COVID-19 does not have features of an eradicable infectious diseases, can still be controlled

Smallpox - eradicated

• No animal reservoir
• Clear pathogenic features
• Short period of infectiousness
• Immune for life, highly effective vaccine

COVID-19 – will get under control

• COVID-19 looks like other respiratory illnesses
• Can spread when presymptomatic
• Found in animals
• Highly effective vaccine for severe disease; increasingly non-sterilizing with variants

We won’t eradicate covid. The pandemic will still end.

By Monica Gandhi

The Washington Post
September 21, 2021
Comes under control/elimination with vaccines (measles) and vaccines/treatment (pertussis)

COVID-19 has vaccines from age of 5 onwards now (prevention) and oral antivirals as of December 2021 (molnupiravir, Paxlovid)
The Atlantic

Ideas

The New COVID Drugs Are a Bigger Deal Than People Realize

Vaccines are amazing, but people who become infected need effective treatments.
Merck and Ridgeback’s Investigational Oral Antiviral Molnupiravir Reduced the Risk of Hospitalization or Death by Approximately 50 Percent Compared to Placebo for Patients with Mild or Moderate COVID-19 in Positive Interim Analysis of Phase 3 Study

10/1/2021

“MOVe-OUT”

- Outpatients with mild-moderate COVID (O2 sat ≥93%)
  - Symptom onset w/in 5 days
  - One or more risk factors for severe COVID (including age>60, obesity, diabetes, CAD)
  - 800mg BID x 5 days vs Placebo
- Interim analysis of 1443 patients of planned n=1550
- Latin America (55%), Europe (23%), Africa (15%) in addition to US
- 30% reduction in all-cause hospitalization/death
  - No deaths in MOV vs 8 deaths PCBO
- Adverse events: 35% vs 40%, Drug related 12% vs 11%, D/c due to AE 1.3% vs 3.4%
- Viral sequencing in 40%: similar efficacy in Delta, Gamma & Mu
Protease inhibitor (Antiviral) for SARS-CoV-2: PF-07321332 (‘332) + ritonavir= PAXLOVID

- Oral SARS CoV-2-3CL protease inhibitor (given with ritonavir)
- Phase 2/3 EPIC trial in high-risk non-hospitalized patients
- Randomized to receive ‘332/rtv (3 pills) every 12 h or placebo, 5 days
- Interim analysis of patients treated within 3 days of symptom onset (n=774)
- Similar reductions in hospitalization or death among people treated within 5 days of symptom onset (n=1219)
- Also being evaluated in lower risk patients and for post-exposure prophylaxis

<table>
<thead>
<tr>
<th></th>
<th>Hospitalization or death</th>
<th>% Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>332/rtv</td>
<td>3/389 (0.8%) 0 deaths</td>
<td>89% P&lt;0.0001</td>
</tr>
<tr>
<td>Placebo</td>
<td>27/385 (7%) 7 deaths</td>
<td></td>
</tr>
</tbody>
</table>

Owen DR et al, Science, 2021
3 trials for Paxlovid

- **EPIC-HR**: Unvaccinated at high risk of severe disease → 89% protection from hospitalization/death
- **EPIC-SR**: Unvaccinated at standard risk of severe disease → (Interim results) – 70% protection from hospitalization/death
- **EPIC-PEP**: Household members of those infected → No efficacy in preventing infection

Unvaccinated at high risk of severe disease
Unvaccinated at standard risk of severe disease
Household members of those infected
Monoclonal antibodies for prophylaxis

Fact Sheet for Patients, Parents And Caregivers: Emergency Use Authorization (EUA) of EVUSHELD™ (tixagevimab co-packaged with cilgavimab) for Coronavirus Disease 2019 (COVID-19)

18 February 2022

Prospective evaluation of COVID-19 vaccine responses across a broad spectrum of immunocompromising conditions: the COVICS study

Ghady Haidar, MD, Mounzer Agha, MD, Andrew Bilderback, MS,

mRNA vaccines work well against range of immunocompromising conditions, but 6 month monoclonal antibody infusion protects
A Rational Roadmap to Future COVID Management

10 point plan

1) Stop mass asymptomatic testing, but focused testing of vulnerable & wastewater surveillance
2) Stop quarantines but isolation when sick (COVID 5 days & paid sick leave)
3) Invest heavily in test and treat program with oral antivirals
4) Stop vaccine passports
5) Space out initial doses of vaccine by 8 weeks in those <40
6) Rational approach to vax boosters in vulnerable; acknowledge hybrid immunity
7) Novavax and Covaxin approval in US along with mRNA vaccines
8) Long COVID and vaccination: Good studies showing vax brings to baseline
9) Ventilate indoor spaces
10) Retire mask mandates but recommend fit/filtered masks inside with high cases
President’s plan for endemic management March 2

1. Vaccines, decide on vaccine booster strategy, new vaccines
2. Prophylaxis with monoclonal antibodies for immunocompromised; Test and treat for those with COVID at high risk with oral antivirals
3. Wastewater surveillance to see if cases going up; pandemic recovery schools, offices
4. Vaccinate world
CDC changed criteria for masking guidance to be based on hospitalizations in your region Feb 24, 2022

COVID-19 Community Levels in US by County

<table>
<thead>
<tr>
<th>Level</th>
<th>Total</th>
<th>Percent</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>79</td>
<td>2.45%</td>
<td>0.71%</td>
</tr>
<tr>
<td>Medium</td>
<td>318</td>
<td>9.86%</td>
<td>1.86%</td>
</tr>
<tr>
<td>Low</td>
<td>2827</td>
<td>87.69%</td>
<td>-2.57%</td>
</tr>
</tbody>
</table>

How are COVID-19 Community Levels calculated?
Uniting Infectious Disease and Physical Science Principles on the Importance of Face Masks for COVID-19

Monica Gandhi¹,* and Linsey C. Marr²

January 2021

**Two major principles.. FIT AND FILTRATION**

- N95
- FFP2
- KN95
- KF94
- Double mask
- Cloth mask with filter

With an endemic virus and vaccines- likely to be optional for personal protection

Analysis of mask “mandates” didn’t find changed spread much likely because type of masks, compliance

CDC data: States with or without mask mandates during Omicron
How can medical providers help with public health response?

1. Harm reduction approach needed for any pandemic
2. Lancet report that strongest predictor of mortality from COVID - rates of vaccination & boosting in elderly
3. School closures did harm to the young & increased non-COVID related deaths in this population (overdoses, homicide, road-related injuries, alcohol)
Physician trust high – 1:1 interactions

- Trust in medical system (not public health) increased during the pandemic
- Patients trust their provider when advising on the vaccines
- Therapeutics now available
  - EVUSHELD for those who are immunosuppressed
  - Antivirals – Paxlovid and Molnupiravir
PFIZER AND BIONTECH ANNOUNCE POSITIVE TOPLINE RESULTS FROM PIVOTAL TRIAL OF COVID-19 VACCINE IN CHILDREN 5 TO 11 YEARS

September 20, 2021

- Results are the first from a pivotal trial of any COVID-19 vaccine in children under 12 years of age
- In participants 5 to 11 years of age, the vaccine was safe, well tolerated and showed robust neutralizing antibody responses
- Companies plan to submit these data to the FDA, EMA and other regulatory agencies around the world as soon as possible
- Results in children under 5 years of age are expected as soon as later this year

No severe disease in either group; 3 infections with vaccine, 16 with placebo (90.7% efficacy)

Pfizer Shot Is Far Less Effective in 5- to 11-Year-Olds Than in Older Kids, New Data Show

February 28, 2022

While protection against hospitalization is still strong, the vaccine offered almost no protection against infection, even just a month after full vaccination.

- Much more immunity by then from exposures
- Doses not spaced out for 5-11 year olds (10 micrograms x 2 3 weeks apart)
- One dose after natural infection?
- During Omicron, less effective with antibodies, strong B/T cell immunity
- 28% US children 2-dose vaccine (34% 1-dose)
Where are we with vaccines under 5?

Pfizer 3-micrograms doses (x 2 3 weeks apart) for those under 5 only appropriately generated an immune response for 6 months-2 years but not 2-4 yrs

Moderna 6 mo-6 (25 micrograms x 2 4 weeks apart) generated good antibodies but prevented 37, 44% of all infections although no hospitalizations (in either group) – to be reviewed in June

Ocugen (Covaxin) vaccine (whole inactivated) applied to FDA from ages 2 onwards on November 5 but not approved yet

Pregnancy vaccination – 57% of infants still had SARS-CoV-2 antibodies at 6 months after vaccination in pregnancy
Revisiting COVID-19 policies: 10 evidence-based recommendations for where to go from here

BMC Public Health

Halperin D....Gandhi M

MITIGATING THE COVID-19 PANDEMIC

- Prepare for future pandemics
- Accelerate vaccination
- Ease restrictions accordingly
- Emphasize education and harm reduction
- Encourage outdoor activities
- Reopen schools
- Avoid lockdowns
- De-emphasize ineffective prevention measures
- Reassess testing
- Expand treatment and prophylaxis
Conclusion

• COVID-19 unfortunately not eradicable by its properties
• Goal is control
• Worldwide strategy is vaccination but US strategy is vaccination + therapeutics and latter should be made available worldwide too
• More treatments coming
• Will always be a medical problem for us (like influenza)

More uniformly infectious, more treatable, more genetically predictable: How coronavirus is getting closer to flu