

## Safe Return to School during the Pandemic: Bringing the Science behind COVID-19 Infection Prevention to the Classroom

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## Disclosures

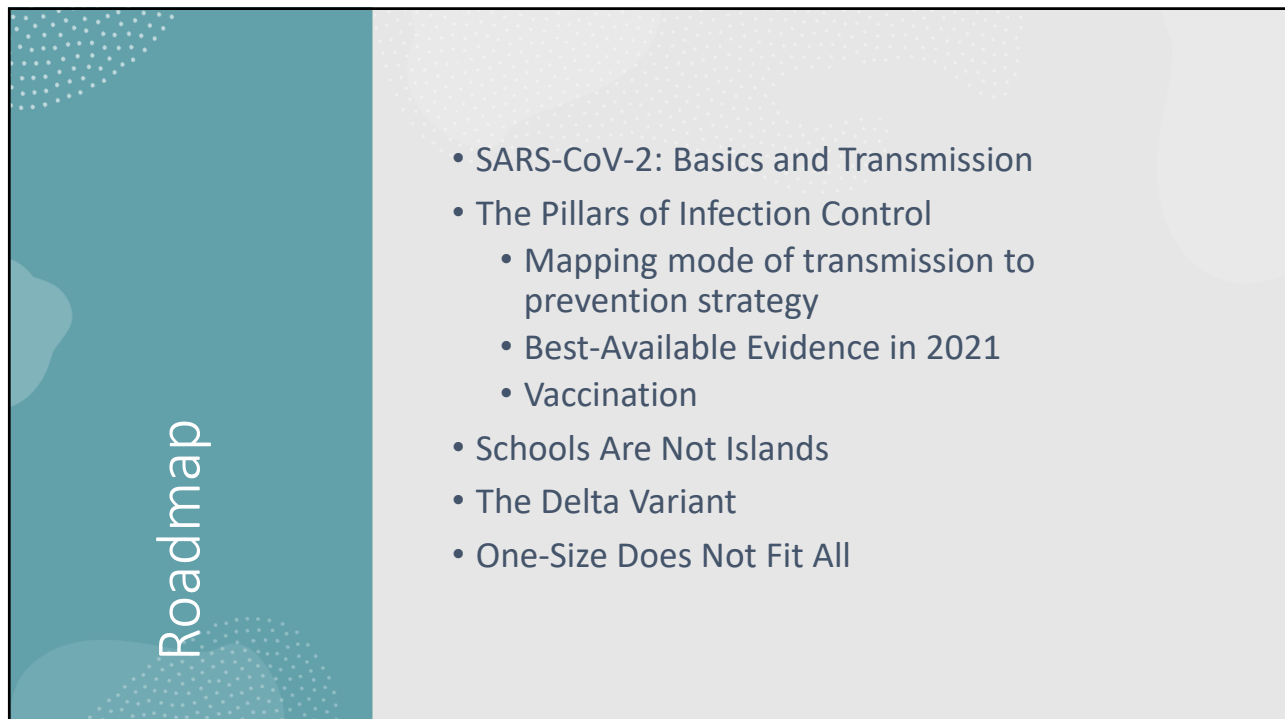
- Site PI for COVID-19 study funded by Gilead Pharmaceuticals (funds to institution)
- Recipient of funding from VA Health Services Research and Development Service and the NIH National Heart Lung and Blood Institute during the past three years

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## Poll: What Do You Think about Full, In-Person School in the Fall

- I am completely comfortable returning
- I am worried about returning, but think it is still the best thing to do
- Schools should offer a hybrid learning approach as a middle ground
- With delta, I think schools should operate in remote mode until a vaccine is available for children
- With delta, I think schools should operate in remote mode until the pandemic is fully controlled, whenever that happens

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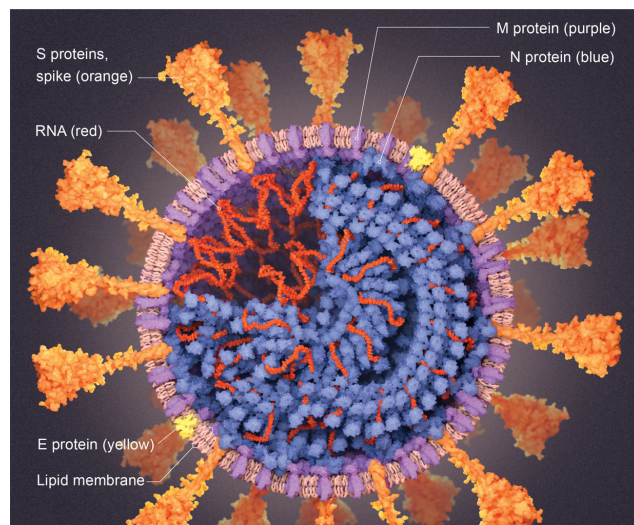
Roadmap

- SARS-CoV-2: Basics and Transmission
- The Pillars of Infection Control
  - Mapping mode of transmission to prevention strategy
  - Best-Available Evidence in 2021
  - Vaccination
- Schools Are Not Islands
- The Delta Variant
- One-Size Does Not Fit All

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## SARS-CoV-2

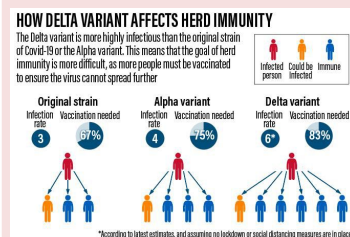
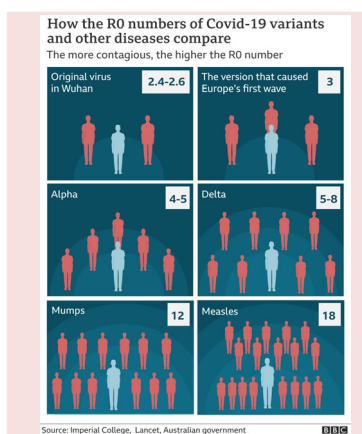
- Novel human coronavirus initially discovered in January 2020
- Rapidly spread worldwide
- Many (thousands) of different coronaviruses
  - Four cause the common cold
    - Immunity partial and short in duration
  - Three cause severe respiratory syndromes
    - SARS-CoV1
    - MERS
    - SARS-CoV2
- Mortality rate highly variable according to age and risk profile
- Kids at substantially lower risk of severe infection and death
- Three vaccines currently approved under EUA for use in the US



Scientific American. A Visual Guide to SARS-CoV-2. 2020  
Edney et al. Bloomberg News. 8/10/2020

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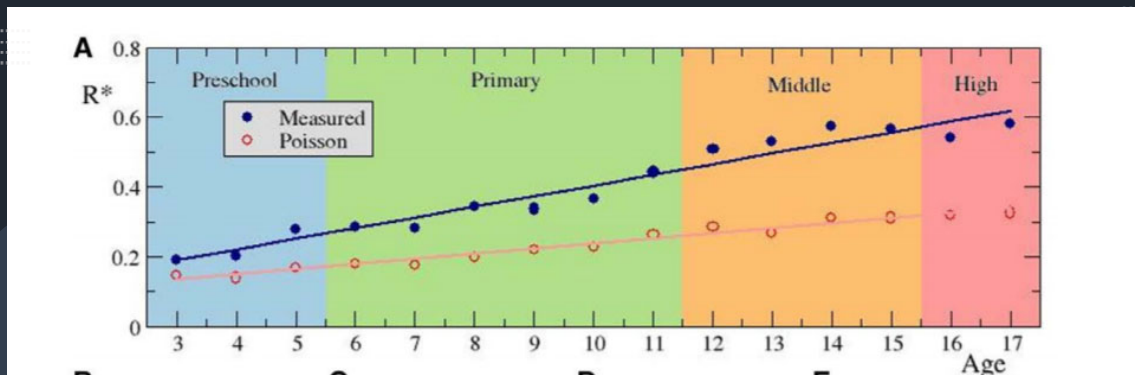
## The Delta Variant



Sources: BBC, NationalNews.Com

- More transmissible than wild-type or alpha
- Vaccines continue to be extremely effective for preventing severe disease and death
- Vaccines also reduce the probability of infection and also reduce the chances of transmission if you are infected
  - Less culturable virus
  - Shorter duration of viral shedding

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## Age and the Risk of COVID-19 Transmission

- Cohort study in Spain
- Children in bubbles and all children in the bubble tested
- Overall R0 in schools 0.4
  - R0 correlated strongly with student age- R0 = 0.2 for younger children, up to 0.6 for high-school aged children
- Masks for age 6 and up (not for <6)

Sergio et al, *Ped Infect J*, July 2021.  
[https://journals.lww.com/pidj/Abstract/9000/Age\\_dependency\\_of\\_the\\_Propagation\\_Rate\\_of.95714.aspx](https://journals.lww.com/pidj/Abstract/9000/Age_dependency_of_the_Propagation_Rate_of.95714.aspx)

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## Long COVID in Children and Adolescents: What Do We Know?

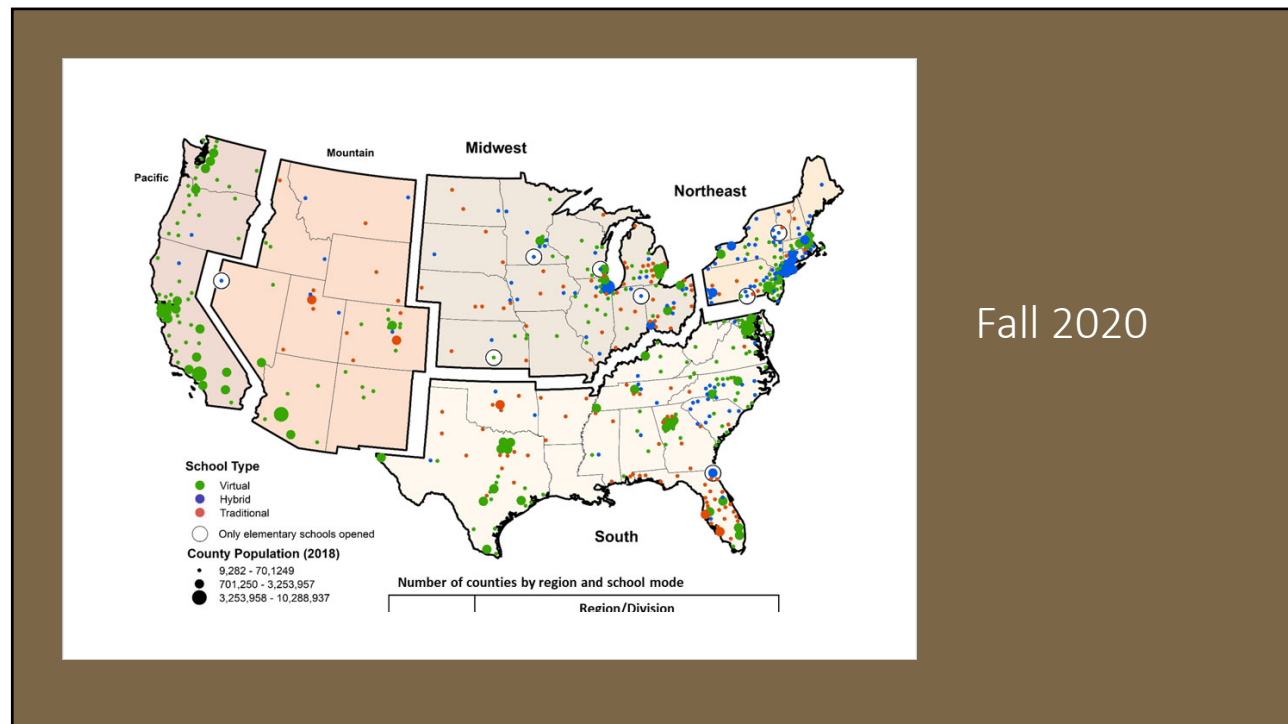
Source: Radke et al, JAMA. July 15, 2021.  
<https://jamanetwork.com/journals/jama/fullarticle/2782164#jld210046t1>

	No. (%)	
	Seropositive (n = 109)	Seronegative (n = 1246)
Female sex	58 (53)	669 (54)
Age, y		
6-11	66 (61)	703 (56)
12-16	43 (39)	543 (44)
≥1 Symptom lasting >12 wk	4 (4)	28 (2)
Tiredness	3 (3)	10 (1)
Difficulty concentrating	2 (2)	8 (1)
Increased need for sleep	2 (2)	0
Congested or runny nose	1 (1)	3 (<1)
Stomachache	1 (1)	3 (<1)
Chest tightness	1 (1)	0
≥1 Symptom lasting >4 wk	10 (9)	121 (10)
Tiredness	7 (6)	51 (4)
Headache	5 (5)	39 (3)
Congested or runny nose	3 (3)	40 (3)
Stomachache	3 (3)	18 (1)
Sleep disturbances	3 (3)	14 (1)
Cough	2 (2)	15 (1)
Self-rated health <sup>a</sup>		
Excellent	43 (41)	497 (41)
Good	56 (53)	680 (55)
Fair	5 (5)	48 (4)
Poor	2 (2)	2 (<1)

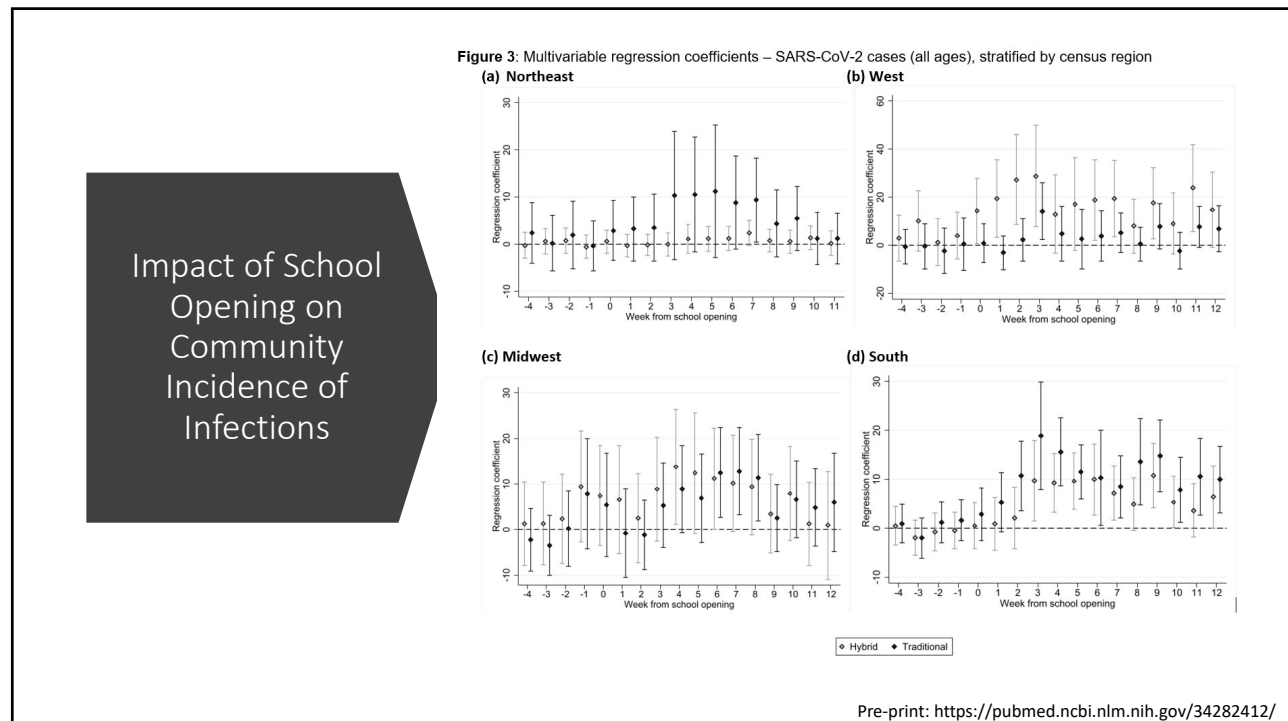
<sup>a</sup> The item self-rated health was assessed with the Health Behavior in School-Aged Children-Survey Instrument (eMethods in the Supplement). Self-rated health was not reported for 3 seropositive and 19 seronegative

- Randomly selected population of schools in Switzerland (N=55)
- Compared a sample of students with evidence of prior COVID (serologic testing) versus those without prior COVID
- Questionnaire to evaluate presence of symptoms
- Found similar rates of symptoms lasting >12 weeks in both groups
  - Tiredness and difficulty concentrating two most commonly reported symptoms

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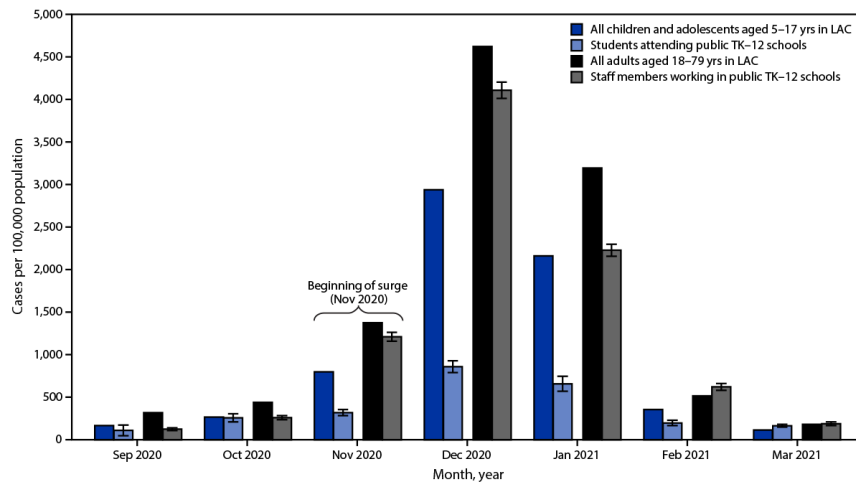


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## LA County: Cases among Students Participating in In-Person Learning

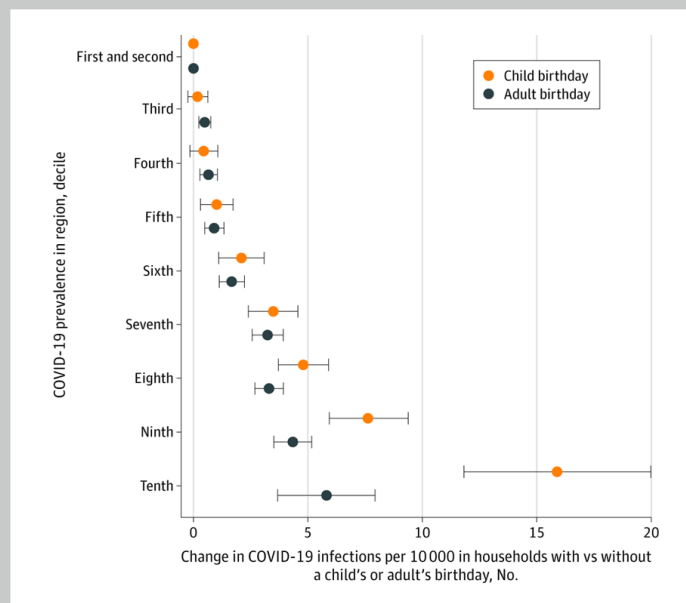


[https://www.cdc.gov/mmwr/volumes/70/wr/mm7035e3.htm?s\\_cid=mm7035e3\\_w#F1\\_down](https://www.cdc.gov/mmwr/volumes/70/wr/mm7035e3.htm?s_cid=mm7035e3_w#F1_down)

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### Its Not Just about What Happens Inside of Schools – We also Have to Think about What Happens Outside of them

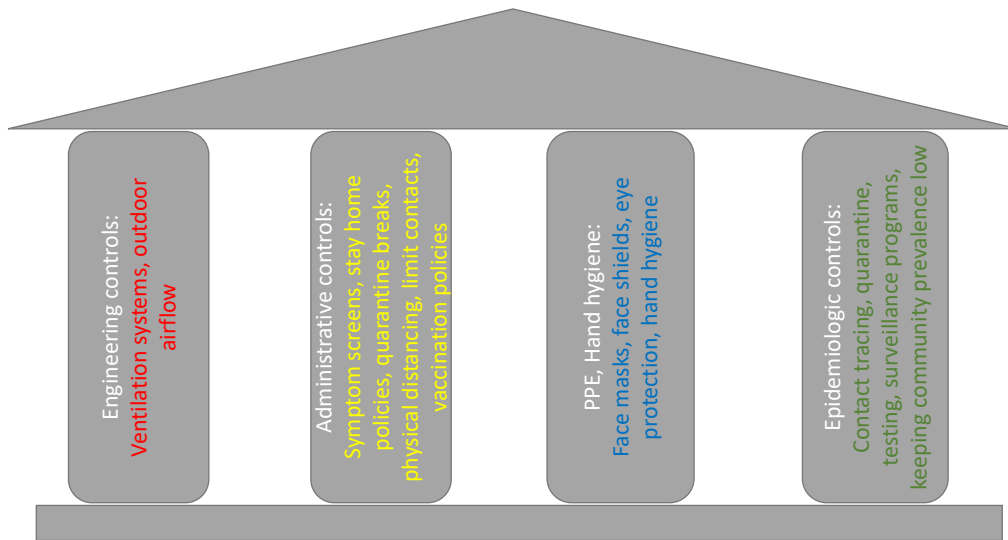
- Administrative health care data on 2.9 million households from the first 45 weeks of 2020
- Among households in the top decile of county COVID-19 prevalence, those with birthdays had 8.6 more diagnoses per 10 000 individuals compared with households without a birthday, a relative increase of 31% of county-level prevalence
- An increase in COVID-19 diagnoses of 15.8 per 10 000 persons after a child birthday
- Increase in COVID-19 diagnoses of 5.8 per 10 000 among households with an adult birthday



Whaley et al. JAMA Int Med, 2021.  
<https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2781306>

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## The Pillars of Infection Control: COVID 2020



Branch-Elliman et al. Curr Envir Health Report. 2015

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## The Tools in Our Arsenal: Linking Mode of Transmission to Infection Control Strategy

Mode of Transmission	Engineering and Environmental Controls	Administrative Controls	Epidemiologic Controls	Hand Hygiene and PPE
Contact/ Environmental	Antimicrobial surfaces (e.g., copper), environmental cleaning	Policies about staying home when sick, no shared food, symptom screens	Contact tracing and quarantine	Hand hygiene, gowns/gloves
Large droplet ( $\geq 5$ microns) (May include ocular)	Environmental cleaning	Policies about staying home when sick, mandatory vaccination, social distancing, symptom screens, limiting contacts	Vaccination Contact tracing, quarantine, post-exposure prophylaxis	Surgical masks, consider eye protection Hand hygiene
Airborne	Ventilation systems (negative pressure, filters), including the use of natural airflow	Policies, such as mandatory vaccination, quarantine periods for exposed individuals, symptom screens, limiting contacts	Vaccination, contact tracing	N95/PPARs

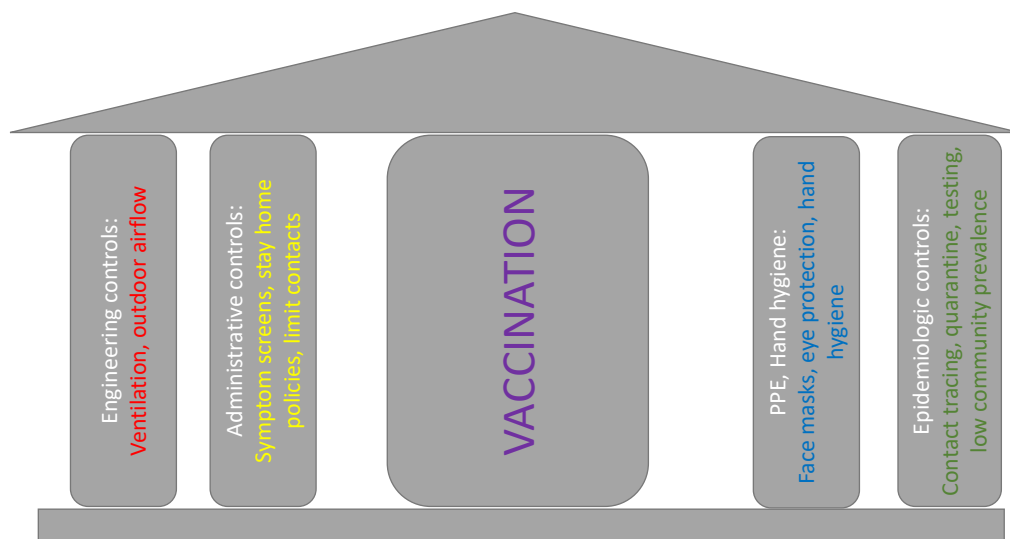
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## Lining up the Infection Control Strategy with the Mode of Transmission: Examples

Pathogen	Mode of Transmission	Infection Control Strategies
Measles	Airborne	Ventilation (negative pressure) Masks (N95s) Vaccination Contact tracing Hand hygiene
Influenza	Droplet, mucus membranes (eyes), contact	Eye protection Medical masks Vaccination Post-exposure prophylaxis Contact tracing Hand hygiene Environmental cleaning
Norovirus	Contact	Environmental cleaning Hand hygiene Avoidance of shared food

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## The Pillars of Infection Control: COVID 2021



Branch-Elliman et al. Curr Envir Health Report. 2015


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## Poll: What Are Your Thoughts about a Pediatric Vaccine and In-Person School?

- Game changer
- Important piece of the puzzle, but not the only one
- Not as important as other things
- Other

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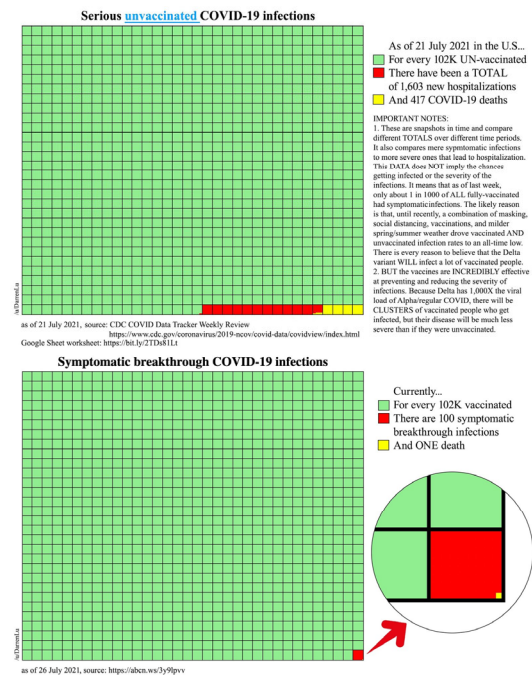


The Most Important Pillar:  
Vaccination

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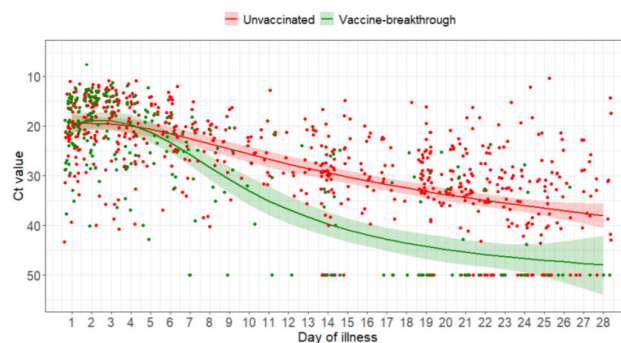
## Vaccine Effectiveness Over Time

- Vaccines remain highly effective at preventing severe disease and death – the major outcomes we are concerned about
  - This is also true of the delta variant
  - mRNA vaccines appear to be more effective than the Janssen vaccine
  - Some patients, particularly those with weakened immune systems have less protection with the standard dose regimen than the general population
    - Israel and France offering booster vaccinations for these populations
    - ACIP has endorsed a booster vaccine
    - Awaiting FDA approval



Source: <https://www.reddit.com/r/dataisbeautiful/>

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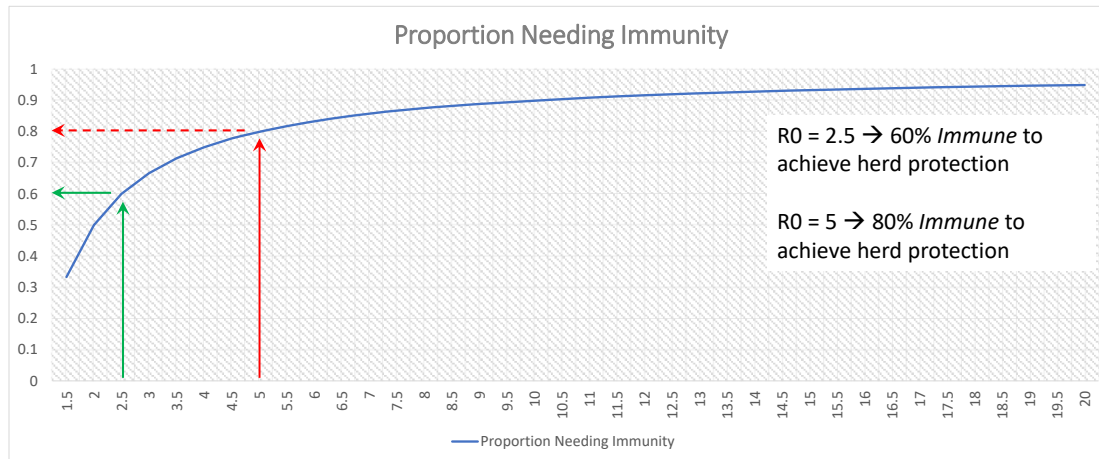
299 **Figure 1:** Scatterplot of Ct values and marginal effect of day of illness of COVID-19 B.1.617.2 infected  
 300 patients with 95% confidence intervals from generalized additive mixed model with interaction term  
 301 between vaccination status and day of illness

Vaccination  
 Reduces  
 Chances of  
 Transmission,  
 Even if  
 Infection Does  
 Occur\*

Pre-print available at: <https://www.medrxiv.org/content/10.1101/2021.07.28.21261295v1>

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# Herd Protection: What Level of Vaccination is Enough?



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## Natural Immunity following Infection: Vaccination Remains the Preferred Strategy!

- Israeli study (pre-print)
- Compared protection provided by previous infection to protection provided by vaccination
- Found that natural immunity was protective against re-infection
- Ongoing considerations of whether documentation of previous infection should confer the same status as vaccination for the purposes of quarantine rules and school-level masking

Variable	Category	$\beta$	OR	95%CI	P-value
Induced Immunity	Previously infected	Ref			
	Vaccinated	1.78	5.96	4.85 - 7.33	<0.001
SES		0.07	1.07	1.03 - 1.11	<0.001
Age group, yr.					
	16-39	Ref			
	40-59	0.06	1.06	0.9 - 1.26	0.481
	≥60	0.79	2.2	1.66 - 2.92	<0.001
Sex					
	Female	Ref			
	Male	-0.01	0.99	0.85 - 1.14	0.842
Comorbidities					
	Obesity (BMI>30)	0.12	1.13	0.94 - 1.36	0.202
	Diabetes mellitus	-0.15	0.86	0.61 - 1.22	0.4
	Hypertension	-0.12	0.89	0.67 - 1.17	0.402
	Cancer	0.2	1.22	0.85 - 1.76	0.283
	CKD	0.3	1.35	0.85 - 2.14	0.207
	COPD	0.48	1.62	0.88 - 2.97	0.121
	Immunosuppression	-0.03	0.98	0.57 - 1.66	0.925
	Cardiovascular diseases	0.08	1.09	0.77 - 1.53	0.638

OR = Odds Ratio; SES = Socioeconomic status on a scale from 1 (lowest) to 10; CVD =

Cardiovascular Diseases; CKD = Chronic Kidney Disease; COPD = Chronic Obstructive Pulmonary Disease.

<https://www.medrxiv.org/content/10.1101/2021.08.24.21262415v1.full-text>

<https://www.sciencemag.org/news/2021/08/having-sars-cov-2-once-confers-much-greater-immunity-vaccine-vaccination-remains-vital>

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## Vaccine Recommendations for Ages 12-17

- In the US, recommended for all eligible children in this age range
- Pfizer vaccine only one available for adolescents in the United States
- Europe recently approved Moderna vaccine for this age group
- India initiating trial of Novavax for children (unclear when this will start)
- Other countries have adopted different standards
  - Germany, Norway recommending vaccination only for 12-17 year olds with higher than normal risk of severe disease

<https://www.reuters.com/business/healthcare-pharmaceuticals/countries-vaccinating-children-against-covid-19-2021-06-29/>

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## Vaccination of School-Aged Children: Where are We Now?

- Nearly half of parents of children ages 12-17 say their child has already been vaccinated (41%) or they will get the vaccine right away (6%).
- The vaccination status of children closely mirrors that of parents.
- Parents of younger children who are not yet eligible to be vaccinated continue to take a cautious approach to COVID-19 vaccines, with four in ten parents of children under 12 saying that once a vaccine is authorized for their child's age group they will "wait a while to see how it is working" before getting their child vaccinated.
- A majority (58%) of parents of 12-17 year-olds say their child's school *should not* require students to be vaccinated for COVID-19, and a similar share (54%) of parents of all school-age children say schools should not require vaccination even once the FDA has fully approved the use of a COVID-19 vaccine in children.

<https://www.kff.org/coronavirus-covid-19/poll-finding/kff-covid-19-vaccine-monitor-parents-and-the-pandemic/>

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## Potential Role for Schools in Improving Vaccine Uptake? Parents Weigh In.

- For parents of unvaccinated teens, their top concerns about the COVID-19 vaccine center around the potential for long-term or serious side effects in children.
- Hispanic and Black parents are more likely than White parents to cite concerns that reflect access barriers to vaccination, including not being able to get the vaccine from a trusted place, believing they may have to pay an out-of-pocket cost, or difficulty traveling to a vaccination site.
- A larger share of Hispanic parents than White parents also reports being concerned about needing to take time off work to get their child vaccinated.
- 4/10 parents of children 12-17 say their teen's school provided information about COVID-19 vaccines or encouraged parents to get their children vaccinated.
  - Those who say their school did either one of these things are more likely to say their child has received a COVID-19 vaccine than parents who say their school did not do these things, even after controlling for other demographic factors associated with higher vaccination rates, suggesting that schools could play a role in increasing vaccine uptake among 12-17 year-olds.

<https://www.kff.org/coronavirus-covid-19/poll-finding/kff-covid-19-vaccine-monitor-parents-and-the-pandemic/>

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## School Vaccination Rate as a Metric for Lifting Masking Mandates?

- For high schools, where all students are eligible for vaccination, Massachusetts and Vermont include school-level vaccination rate as a metric for lifting masking mandates
  - Proposed level is 80% for the entire school community
    - Based on  $R_0 \sim 5$  to prevent a cluster → need 80% immune
    - Prior infection likely provides additional herd protection beyond the vaccination rate
  - Masking is ***always*** optional and supported!
    - Metrics relate to lifting mandatory masking – not disallowing masking for those who chose to continue to mask

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## Risk of Myocarditis following mRNA vaccines

- Small risk of myocarditis (inflammation of the heart muscle) following vaccination with mRNA vaccines
- Most cases in adolescent and young males >16 years of age
  - Risk appears to be increased following the second shot
  - Prior COVID infection may be a risk modifier
- Investigations ongoing; ACIP review on 8/30 noted a small increased risk of myocarditis/pericarditis but continues to recommend use for 12-15 year olds

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## But what about a Vaccine for Younger Kids?

- Pfizer announced on July 26<sup>th</sup> plans to double the size of their clinical trial for 5-11 year olds
- Moderna also in active discussions to increase trial size
- Pfizer still anticipates fall submission date for review
  - FDA review several weeks
  - Vaccine roll out
  - Time to effectiveness (~6 weeks)
- Francis Collins: "I've got to be honest, I don't see the approval for kids — 5 to 11 — coming much before the end of 2021."

<https://www.nytimes.com/2021/07/26/us/politics/fda-covid-vaccine-trials-children.html>

<https://www.npr.org/sections/back-to-school-live-updates/2021/08/24/1030611406/a-vaccine-for-young-children-is-not-likely-until-the-end-of-year-nih-director-sa>

The FDA has asked the companies to include 2,000 children in the 5-to-11-year-old group, the group for whom results were expected first, according to people familiar with the situation. One of the people, granted anonymity to speak freely, described that figure as double the original number of study participants.

A spokesman for Moderna, Ray Jordan, confirmed that the company intends to expand its trial "to enroll a larger safety database which increases the likelihood of detecting rarer events" and expects to seek emergency authorization late this year or early next year.

The Moderna trial began recruiting patients in March with the aim of enrolling 6,705 participants younger than 12. The participants were to be split equally into three age brackets, including a 6 to 11 year old group, of 2,265 participants each. Mr. Jordan said the company is "actively discussing" a proposal with the F.D.A. to expand the trial.

Pfizer is on a faster timetable than Moderna, and may be able to meet the F.D.A.'s expectations on a bigger trial size and still file a request to expand emergency authorization of its vaccine by the end of September. Reviewing all the safety and efficacy data will likely take regulators at least a few weeks.

At the F.D.A.'s urging, Pfizer-BioNTech and Moderna are expanding their trials for children 5 to 11.



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## Other Considerations

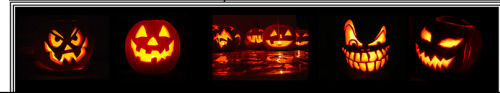
- Pre-Screening Programs
  - Adopt from hospital settings
  - Online or app-based
- Mandatory Vaccination Programs
  - Including influenza



**DON'T GET SPOOKED BY THE FLU.**  
Get your flu vaccine before Halloween!



Say Boo To The Flu



Boston Globe. August 20, 2020. Flu Shot Mandate Leaves Key Questions Unanswered.

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Ventilation

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## Poll: How Long Should Elementary School Kids Wear Masks in Indoor Settings?

- Until a vaccine is available
- Until community prevalence hits a low enough level and most of the adults around them are vaccinated
- They should stop now
- Masks should always be used in schools from now on

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Table 1. Comparison of Respiratory Virus Transmission Outdoors Compared to Indoors Ordered by Virus Studied

Outcome	Virus Studied	Estimate of Effect		Relative Estimate of Effect	Number of Participants in the Study
		Outdoor	Indoor		
Number of cases [14]	SARS-CoV-2	2/7324 cases	7322/7324 cases	<1% of transmissions happened outdoors	7324 cases, totaling 318 outbreaks
Number of cases [15]	SARS-CoV-2	4/103 cases	99/103 cases	5% of work-related cases occurred outdoors	103 possible work-related cases at a total of 690 local transmissions
Odds of transmission [16]	SARS-CoV-2	Raw data not available	Raw data not available	Odds of transmission in closed environments 18.7 (95% CI, 6.0–57.9) times greater than in open air	110 cases: 27 primary cases and 83 secondary cases
Number of super-spreading events and odds of transmission* [16]	SARS-CoV-2	1/7 super-spreading events	6/7 super-spreading events	Odds ratio of super-spreading in closed environments: 32.6 (95% CI, 3.7–289.5)	110 cases: 27 primary cases and 83 secondary cases
Number of cases [17]	SARS-CoV-2	95/10 926 cases	10 831/10 926 cases	<1% of transmissions happened outdoors	10 926 cases, totaling 201 events of transmission
Number of cases [18]	H1N1 2009 influenza	0/3 cases	24/29 cases	Of 32 total people in a holiday camp, 29 traveled together in a train wagon	32 people at a holiday camp
Mortality [19]	H1N1 1918 influenza	28/820 deaths sleeping in hammocks outside, 34.1 persons/1000	39/267 deaths sleeping in cabins inside, 146.1 persons/1000	Risk ratio 4.28 (95% CI, 2.69–6.81)	Total 1217 people on the ship

Abbreviations: CI, confidence interval; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

\*Super-spreading defined as events where the number of secondary cases generated by a single primary case is greater than the 95th percentile of the distribution (ie, transmissibility more persons).

Outdoors  
>>>> Safer  
than Indoors

Bulfone et al, JID, 2021

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## MMWR Georgia Elementary Schools Study

- Survey study of schools in Georgia

- Collected data about mitigation measures and cases in students and staff
- 169 schools with 91,893 students enrolled
- Opening a window associated with a decreased incidence of infections, as was masking of teachers
  - Other interventions (mandatory masking of students, use of air filtration strategies) were not significantly associated with reductions in risk of transmission

Mitigation Measure	Number of Schools	Number of Students	Relative Risk (CI)
None	37	21,844	<i>Referent</i>
<b>Dilution (vs. none)</b>	39	21,562	<b>0.65 (0.43-0.98)</b>
Filtration	16	9,133	0.69 (0.40-1.21)
Dilution and Filtration (vs. none)	31	13,960	0.52 (0.32-0.83)
<b>Universal Masking of Teachers</b>	110	61,190	<b>0.63 (0.47-0.85)</b>
Universal Masking of Students	87	49,132	0.79 (0.50-1.08)

<https://www.cdc.gov/mmwr/volumes/70/wr/mm7021e1.htm>

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## Poll: What Caused the Marin County Cluster

- A: Lack of masking mandate
- B: Working while sick and symptomatic
- C: Unvaccinated teacher
- A and B
- B and C
- A, B, and C

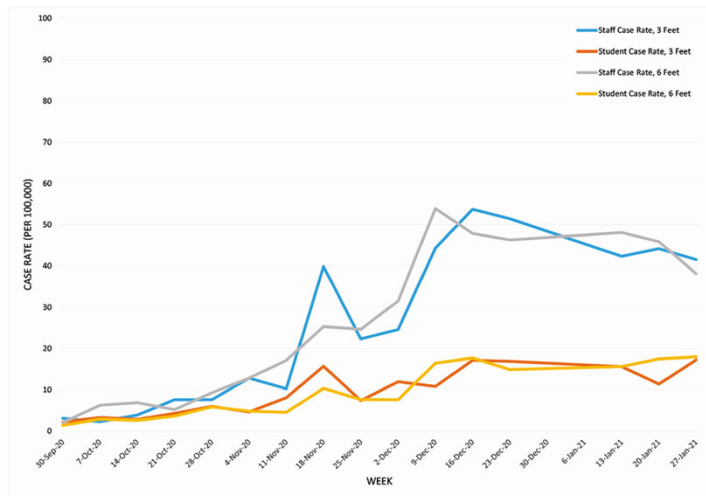
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<https://www.cdc.gov/mmwr/volumes/70/wr/mm7035e2.htm>

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## Physical Distancing: No Impact on Cases in Multiple States

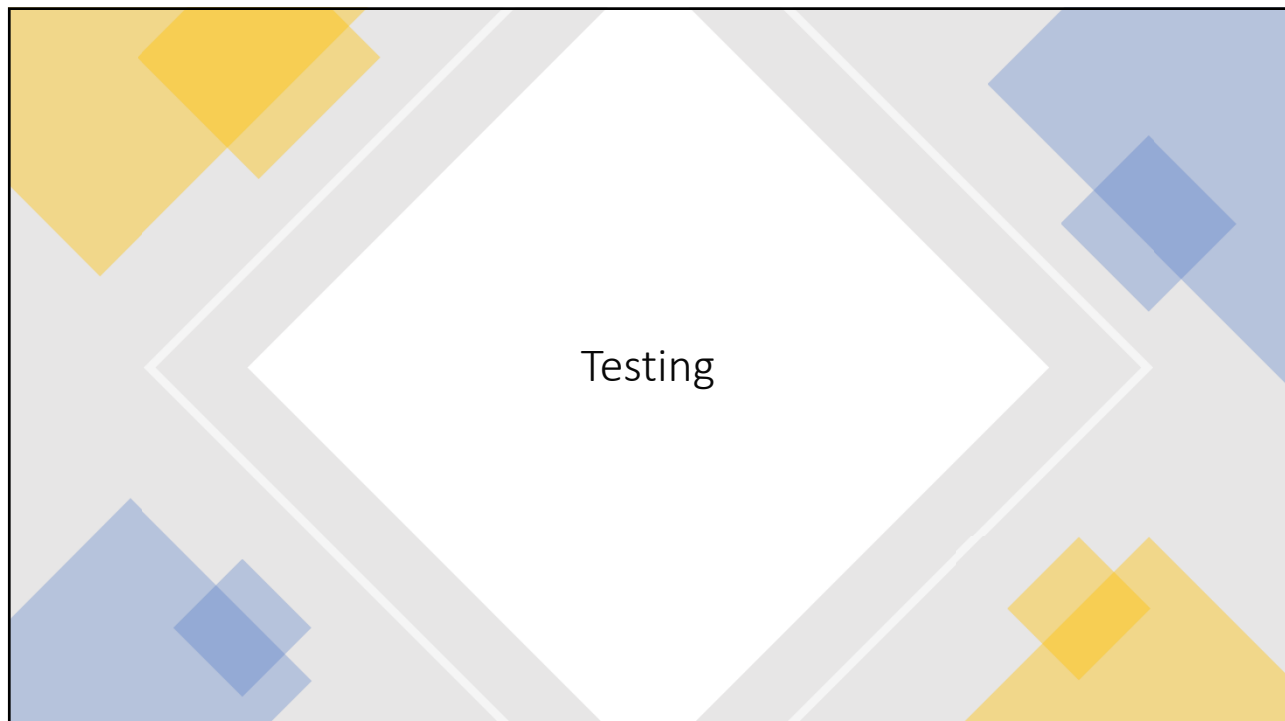
- Similar findings from Utah, North Carolina, among others
  - NC: No difference in cases at any level of distance
- NC study also found no impact on distancing on school buses



Van den Berg et al, *Clinical Infectious Diseases*, 2021.

<https://abcsciencecollaborative.org/wp-content/uploads/2021/06/ABCs-Final-Report-June-2021.06-esig-DB-KZ-6-29-21.pdf>

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## What Do You Think about Screening Testing?

- Screening testing is one of the most important strategies for preventing transmissions in schools
- Screening testing has both benefits (finding a lot of cases) and downsides (keeps children out of schools)
- Screening testing is not worth it in low prevalence settings – too many false positive results causing unnecessary school closure and quarantine

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### Screening Testing

- Utility of a clinical test depends upon the pre-test probability of having a disease
- Last year in Massachusetts, 0.7% of pools positive, each representing 5-10 individuals
- Assuming a prevalence of 0.1% (what we saw last year), and a near-perfect test (PCR), screening testing will identify 14 false positive cases for every true positive case
- Once the prevalence increases to 2%, the predictive value changes dramatically
  - Consideration for diagnostic testing in schools for symptomatic children to rapidly guide decisions about test-to-stay and/or quarantine

Utility of Screening Testing for SARS-CoV-2: Impact of Population Prevalence on False Positive Rate

Population Disease Prevalence	Number of True Positives*	Number of False Positives**	Positive Predictive Value of a Positive Test (Probability a Positive Test Represents a True Case)	Approximate Ratio of False Positives to True Positives	Number of False Positives	Positive Predictive Value of a Positive Test	Approximate Ratio of False Positives to True Positives
		95% Specificity***				99% Specificity***	
0.5%	35	495.7	6.57%	~14:1	99.5	26%	~2.8
0.1%	7	499.5	0.197%	~71:1	99.9	6.55%	~14

\*For the purposes of these calculations, we assumed 70% sensitivity, the approximate estimate for PCR-based SARS-CoV-2 testing. Sensitivity is the proportion of true cases that will be detected by the test.

\*\*We assumed a theoretical cohort of 10,000 individuals, however, the positive predictive value and the ratio would not change if the population was larger or smaller at a given prevalence level.

\*\*\*Specificity was estimated at 95% and 99%. Specificity is the proportion of negative cases that the test identifies as negative.

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## Would you Support Test-to-Stay or Diagnostic Testing in Your School?

- Yes
- No
- Not Sure Yet

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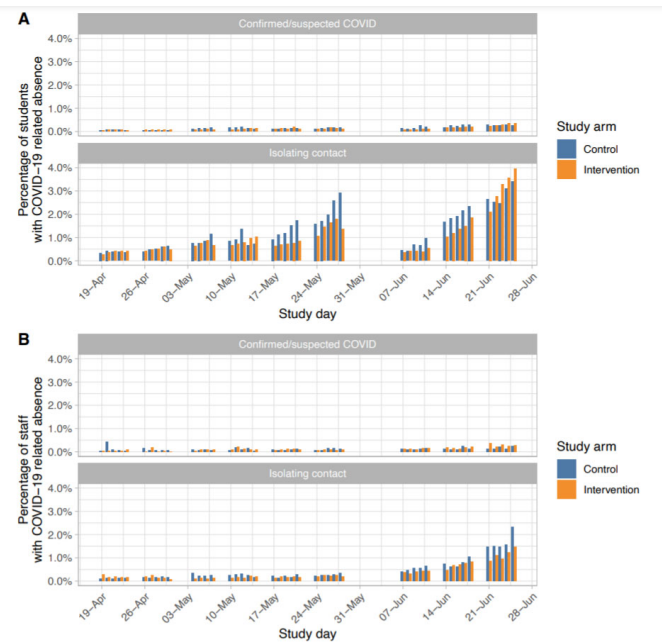
## Testing: Time to Innovate

- Screening in low prevalence settings is likely to be dominated by false positives rather than true positives, and unclear impact on preventing transmissions
  - Decision may be different in areas with higher prevalence of disease, because the positive predictive value of the test will be higher
- Test-to-Stay non-inferior to quarantine and optimizes in-person learning
  - Will need a system for tracking and implementing
- Future testing in schools may include testing not only for COVID but also for other respiratory viruses, as we are likely to see the incidence of other types of respiratory viruses increase as community-level mitigation measures are lifted
  - Seeing increases in reports of other respiratory viruses, including RSV, atypical of seasonality

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## Test-to-Stay: Balancing Safety and In-Person Learning

- Cluster randomized trial of schools in the United Kingdom (pre-print)
- 76 schools in the control arm; 86 in the intervention arm
  - Control → standard quarantine if close contact
  - Intervention → Daily testing with PCR if exposed, stay in school unless positive test
- Non-inferiority design
- Incidence of infections similar in both arms
  - 1.6% in control
  - 1.5% in intervention
- Fewer days of missed school in the intervention arm
- Strategy included in Massachusetts Department of Elementary and Secondary Education (DESE) guidelines for 2021-22



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## Massachusetts Test and Stay Program

Aim is to reduce time spent in quarantine and to maximize in-person learning

Daily testing with Abbott Binax Now (Antigen Test) for at least 5 days following a classroom exposure

Students stay in the classroom as long as test is negative

Testing program also includes optional pooled (screening) testing and diagnostic testing

<https://www.doe.mass.edu/covid19/testing/>

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## How Does Delta Change Things?

- Delta does not change the importance of in-person learning
- Delta is clearly more transmissible than earlier variants, which means a higher proportion of a population will need to be immune to achieve herd protection
  - If  $R_0$  is 5, then ~80% of the population will need to be immune to control the outbreak
  - This will not protect individuals who are not immune, but it will protect the population from large outbreaks
- Vaccines remain extremely effective for preventing severe COVID-19 disease
  - Some populations may need a booster vaccine
- One size will not fit all; a nuanced approach to decision-making and mitigation measures will be needed, based on a variety of factors, including community prevalence and community vaccination rates

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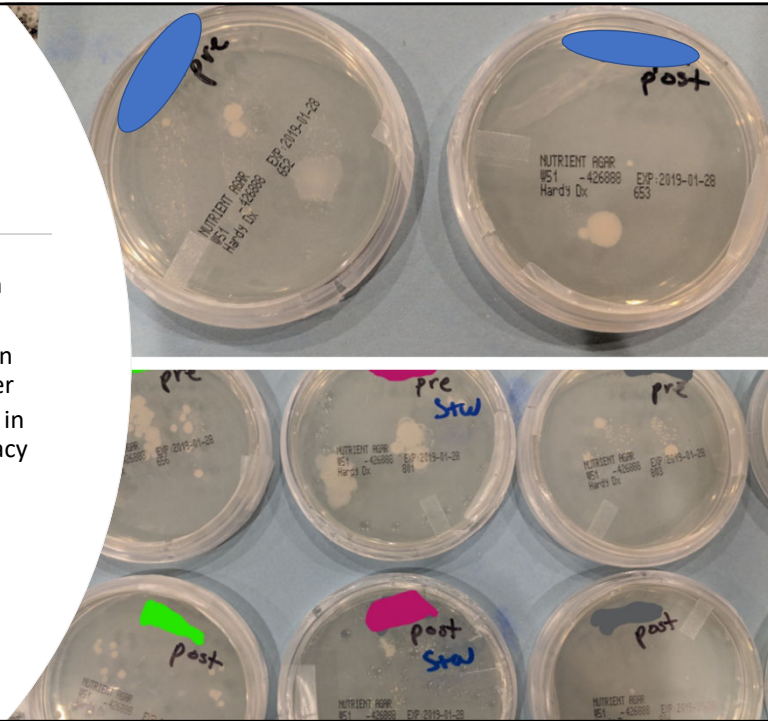
Hand Hygiene: Don't Forget  
the Basics

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## Hand Hygiene: Don't Forget the Basics!

- Soap and water and hand sanitizer both work if done correctly
- Hand sanitizer usually performs better in real-world settings because it is a lot easier
  - Multiple randomized controlled trials in schools demonstrate safety and efficacy
  - Schools that use hand sanitizer with fewer outbreaks of GI illness than schools that have a soap and water policy

Branch-Elliman. The Incidental Economist. August 2020.



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## Lingering Questions

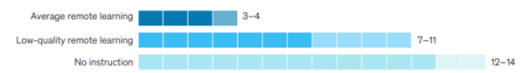
48



Schools are essential and COVID is not the only outcome!

- Increasing pediatric mental health emergency room visits
- Concerns for increasing rates of childhood obesity
- Reduced reporting of child abuse
- Increasing food instability
- Decreasing literacy rates and increasing achievement gaps

**Average months of learning lost in scenario 2 compared with typical in-classroom learning**



NWEA is a K-12 assessment provider serving over 9,500 schools across the US; their RIT scores are a standardized scaled score that measures student performance and progress.

<sup>1</sup>Normal school year growth rates estimated using NWEA data.

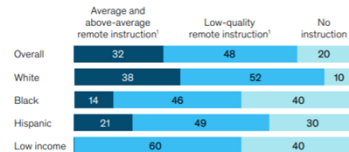
<sup>2</sup>50% assumed growth for high-quality instruction.

<sup>3</sup>0% assumed average growth for low-quality instruction. Rates of learning loss may differ by student groups.

Source: Megan Kuhfeld, Dennis Condon, and Doug Downey, *When does inequality grow?*, 2019; Center for Research on Education Outcomes, Online Charter Schools Study, 2015

Learning loss will probably be greater for low-income, black, and Hispanic students.

Quality level of remote instruction, % of K-12 students



Black, Hispanic, and low-income students are at higher risk of not receiving remote instruction of average or above-average quality ...

Average months of learning lost in scenario 2 compared with typical in-classroom learning<sup>2</sup>



... and the result is learning loss from student disengagement and/or lack of access

<sup>2</sup> Includes 0.05 standard deviation reduction for black, Hispanic, and low-income students to account for recession impacts (~1 month of additional lost learning).

Source: Rand Institute Report, 2021

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Table. Weight Changes in Youths Over an 11-Month Period Before and During the Pandemic<sup>a</sup>

Age group, y	Prepandemic			Pandemic			Δ2-1Δ (95% CI)
	Start	End	Change 1 (Δ1, 95% CI)	Start	End	Change 2 (Δ2, 95% CI)	
Distance from the median BMI for age, mean (SD) <sup>a,c</sup>							
5-11	0.26 (0.03)	0.41 (0.03)	0.15 (0.11 to 0.18)	0.48 (0.03)	2.20 (0.03)	1.72 (1.67 to 1.76)	2.30 (2.23 to 2.3)
12-15	0.52 (0.03)	0.48 (0.03)	-0.03 (-0.07 to -0.00)	0.47 (0.03)	1.34 (0.03)	0.87 (0.83 to 0.91)	2.31 (2.19 to 2.4)
16-17	0.52 (0.05)	0.27 (0.05)	-0.25 (-0.30 to -0.21)	0.30 (0.05)	0.53 (0.05)	0.23 (0.18 to 0.28)	1.02 (0.85 to 1.2)
Body weight, mean (SD), kg <sup>a,c</sup>							
5-11	27.58 (0.04)	27.65 (0.04)	0.07 (0.03 to 0.11)	27.67 (0.04)	30.04 (0.04)	2.37 (2.32 to 2.42)	2.30 (2.23 to 2.3)
12-15	48.73 (0.08)	50.52 (0.08)	1.39 (1.31 to 1.46)	50.34 (0.08)	54.05 (0.08)	3.70 (3.61 to 3.80)	2.15 (2.09 to 2.2)
16-17	59.52 (0.13)	60.14 (0.13)	0.12 (0.91 to 1.13)	60.96 (0.14)	63.00 (0.13)	2.04 (1.91 to 2.18)	2.02 (1.85 to 1.4)
Overweight or obese (≥85th percentile), rate (SD), % <sup>a</sup>							
5-11	34.76 (0.23)	35.70 (0.23)	0.94 (0.58 to 1.30)	36.16 (0.26)	45.74 (0.28)	9.58 (9.01 to 10.16)	8.65 (7.96 to 9.3)
12-15	39.04 (0.31)	38.52 (0.31)	-0.53 (-0.97 to -0.08)	38.74 (0.35)	43.41 (0.34)	4.67 (3.99 to 5.35)	5.19 (4.37 to 6.0)
16-17	37.97 (0.48)	36.57 (0.46)	-1.40 (-2.04 to -0.76)	36.52 (0.50)	38.20 (0.48)	1.67 (0.75 to 2.59)	3.07 (1.94 to 4.2)
Overweight (≥85th to <95th percentile), rate (SD), % <sup>a</sup>							
5-11	17.22 (0.20)	16.87 (0.20)	-0.35 (-0.80 to 0.10)	16.99 (0.26)	18.86 (0.23)	1.87 (1.16 to 2.57)	2.22 (1.37 to 3.0)
12-15	19.23 (0.27)	18.82 (0.27)	-0.41 (-0.98 to 0.16)	19.69 (0.34)	19.35 (0.29)	-0.34 (-1.20 to 0.52)	0.07 (-0.98 to 1)
16-17	19.32 (0.41)	18.00 (0.39)	-1.12 (-1.92 to -0.31)	17.66 (0.46)	17.54 (0.40)	-0.12 (-1.23 to 0.98)	1.00 (-0.39 to 2.3)
Obesity (≥95th percentile), rate (SD), % <sup>a</sup>							
5-11	17.27 (0.18)	18.38 (0.18)	1.11 (0.83 to 1.39)	18.79 (0.21)	26.11 (0.25)	7.32 (6.84 to 7.80)	6.21 (5.66 to 6.7)
12-15	19.19 (0.25)	19.06 (0.25)	-0.13 (-0.47 to 0.22)	18.58 (0.27)	23.20 (0.30)	4.62 (4.06 to 5.18)	4.75 (4.09 to 5.4)
16-17	18.18 (0.37)	17.97 (0.37)	-0.21 (-0.70 to 0.28)	18.41 (0.41)	20.07 (0.41)	1.66 (0.93 to 2.39)	1.89 (0.79 to 2.9)

<sup>a</sup> Total body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) measures included in the models totaled 425 855 from March 2019 to January 2020 (2.22 BMI measures per youth) compared with 283 718 from March 2009 to January 2019 (2.02 BMI measures per youth).

<sup>b</sup> All models are adjusted for race and ethnicity (Asian or Pacific Islander, Hispanic, non-Hispanic Black, non-Hispanic White [reference], and other race), state-subsidized health care [reference, none], parks (no parks,

Estimates are shown for the reference group. After initial decrease, in-person well-child visits were back to 84% of prepandemic visits by June 2020.

<sup>c</sup> Models for distance from the median BMI for age and body weight were also adjusted for baseline weight class (<5th, 5th–84th, 85th–94th, 95th–97th, >97th reference, 5th–≤85th), the model for body weight is adjusted for height.

# Childhood obesity

- Kaiser Cohort, did not evaluate impact of school mode on weight gain
- 191,509 children
- Adjusting for height, a mean weight gain:
  - 5- through 11-year-olds: 2.30 kg (95% CI, 2.24-2.36 kg)
  - 12-15 year olds: 2.31 kg (95% CI, 2.20-2.44 kg)
  - 16 to 17 year olds: 1.03 kg (95% CI, 0.85-1.20 kg)
  - Overweight or obesity increased among 5-through 11-year-olds from 36.2% to 45.7% during the pandemic, an absolute increase of 8.7% and relative increase of 23.8%
  - The absolute increase in overweight or obesity was 5.2% among 12- through 15-year-olds (relative increase, 13.4%) and 3.1% (relative increase, 8.3%) among 16- through 17-year-olds.

<https://jamanetwork.com/journals/jama/fullarticle/2783690#ild210057t1>

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## Poll: What Do You Think about Full, In-Person School in the Fall

- I am completely comfortable returning
- I am worried about returning, but think it is still the best thing to do
- Schools should offer a hybrid learning approach as a middle ground
- With delta, I think schools should operate in remote mode until a vaccine is available for children
- With delta, I think schools should operate in remote mode until the pandemic is fully controlled, whenever that happens

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## Take Home Points

- In-Person learning is critical
- The most effective strategy we have is vaccination of anyone who is eligible
  - Vaccine mandates for adults in school buildings is a strong consideration to protect staff and students
- Opening windows and natural airflow are also strongly protective
- One-Size does not fit all – local data will need to inform best practices
  - It's complicated!
  - Schools are not islands
- Pediatric vaccine availability is unclear; many open questions

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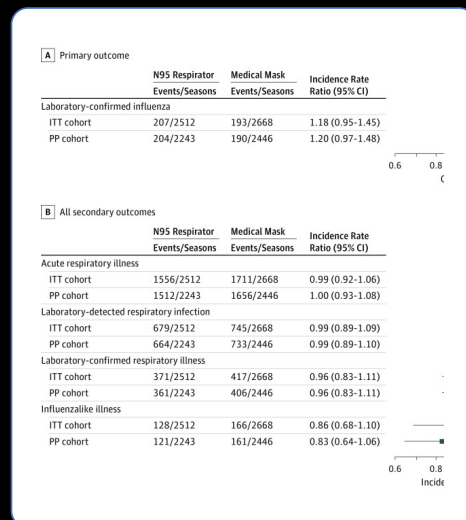


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## But Isn't an N95 always better than a medical mask?

- Cluster randomized trial at 137 outpatient sites
- 1993 participants in 189 clusters randomly assigned to wear N95s during flu season and 2058 participants in 191 clusters were randomized to wear medical masks when near patients with respiratory illness
- Compliance similar in the two groups
  - 89% in N95 versus 90% in mask
- No difference in incidence of laboratory-confirmed disease in either group but a trend toward decreased incidence of URI in the medical mask group

Radonovich et al. JAMA. 2019



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## Spread of COVID-19

- COVID-19 spreads via close contact/droplet transmission with a component of small particle transmission
- Indoor settings with poor ventilation are high risk for transmission and may lead to super-shedding events
  - High risk activities implicated– singing, telephone conference rooms, choirs
  - Typically, limited use of infection control strategies when these events occurred
    - Poor ventilation, no PPE, close contacts, etc.
    - Masking is effective for reducing spread
- Little data to support indirect contact as a significant mode of transmission, but self-inoculation (e.g., eye rubbing) may play a role

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## Testing and Contact Tracing

- Testing and contact tracing are key to outbreak management
  - Rapid results allow a cluster to be identified and contained before it becomes out of control
  - Rapid antigen tests less sensitive than PCR tests, however, a recent study suggests they may be sufficient for outbreak control in college settings
    - Easier to run
    - Faster response time
  - Schools will need a system for obtaining and acting upon testing
    - Community partnerships
    - Academic partnerships
    - Integrated into local communities
      - Sewage testing

	Diagnostic	Screening
Predominant type of test	RNA amplification	Antigen testing
Sample collection	Swab	Swab or saliva
Turnaround time	Days	Minutes
Cost	\$\$\$	\$
Accuracy	High	Moderate
Frequency	Single tests	Multiple tests every week

Sources: Service. Science Magazine. 2020; Kennedy-Shaffer, Lee, Michael Baym, and William Hanage. Perfect as the Enemy of the Good: Using Low-Sensitivity Tests to Mitigate SARS-CoV-2 Outbreaks (2020).

N. DESAI/SCIENCE

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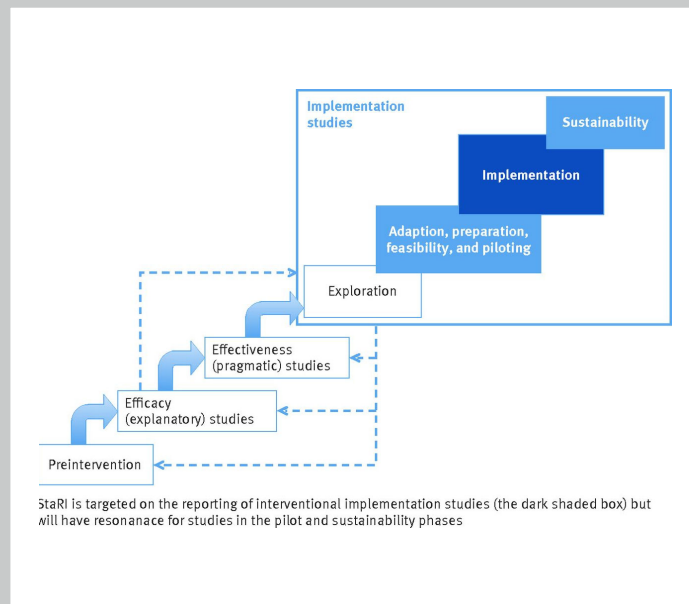
## Don't forget to think about implementation outcomes!

- Implementation Outcomes:

- **Acceptability**
- Adoption
- Appropriateness
- Costs
- **Feasibility**
- **Fidelity**
- **Penetration**
- **Sustainability**

“The single most important concept identified in the management of patients affected by viruses transmitted by the droplet/contact route is the precision of execution in the use of PPE, and which should be the primary focus rather than on the type of mask used by HCWs as a component of PPE.”

Proctor. Adm Policy Ment Health. 2011  
Pinnock et al. STARI. BMJ. 2017  
Conly et al. ARIC. 8/6/2020.



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## Do You *Really* Think Things like Fit and Comfort Are Important?

- Effectiveness of any PPE strategy is dependent upon a variety of factors, including adherence (fidelity) to the intervention
- 73 evidence-based implementation strategies
- Recent data suggests that the more implementation strategies that are used, the more likely an intervention is to succeed
- Also need to consider *sustainability* of the intervention
  - PPE, distancing strategies may be at high risk of “voltage drop” over time

### Mask Effectiveness: $f$ (Filtration capacity \* Fidelity \* Fit)

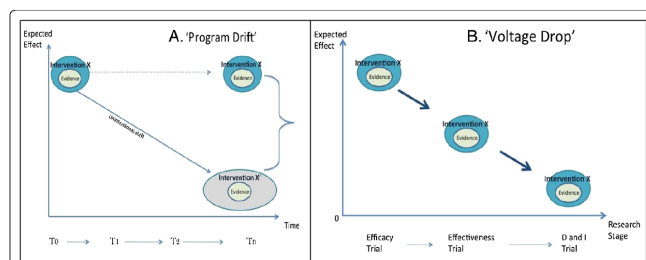


Figure 1. Program drift and voltage drop. Illustration the concept of 'voltage drop' in which the expected effect of an intervention is measured

### Dynamic Sustainability Framework

Chambers. Implementation Science, 2013.  
MacIntyre et al. 2009. Emerging Infectious Diseases

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## Milton Specifics

### Epidemiologic Controls:

- Community prevalence low:
  - Incidence: 3.5 cases/100,000
  - 1.96% test positivity rate
- Evaluating various models to incorporate testing with rapid turnaround of results

### Engineering Controls:

- Evaluating strategies to improve indoor ventilation
- Encouraging use of outdoor spaces
- Testing feasibility of additional infrastructure

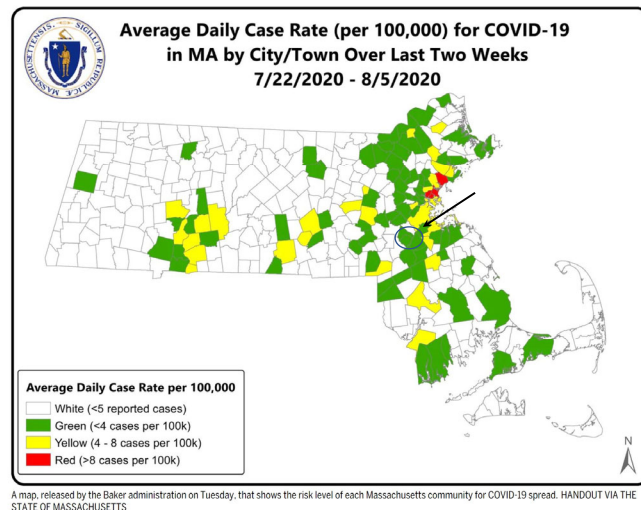
### Administrative Controls:

- Daily symptom screens prior to entry into school buildings
- Physical distancing (6 feet) included in plans
- Updated vaccination policy

### PPE/Hand hygiene:

- PPE provided to teachers the **same** as for healthcare workers caring for confirmed COVID-positive patients in the hospital\*
  - Surgical masks
  - Eye protection recommended
  - Surgical masks available and provided to children who need them
- Hand sanitizing stations and education
- PPE plan designed to be feasible and acceptable, and to encourage compliance and sustainability

\*Conly et al. ARIC. 8/6/2020.

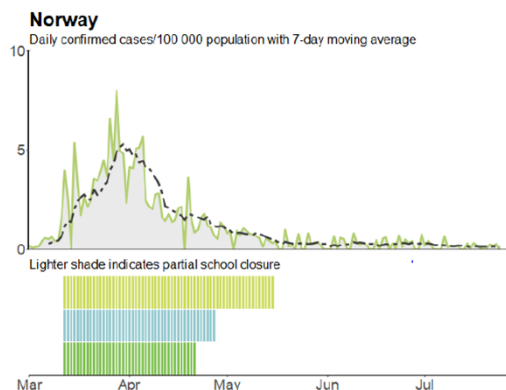


From: The Boston Globe: [https://www.bostonglobe.com/2020/08/11/nation/heres-look-new-state-map-high-moderate-low-risk-communities-covid-19-mass/?p1=Article Inline\\_Text\\_Link](https://www.bostonglobe.com/2020/08/11/nation/heres-look-new-state-map-high-moderate-low-risk-communities-covid-19-mass/?p1=Article Inline_Text_Link)  
Accessed 8/12/2020.

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## What can we learn about what happened in other countries and settings?

- As of June, more than 20 countries re-opened schools
- In most cases, no significant uptick in community spread after a careful re-opening
  - Different countries adopted various infection control strategies
  - Common themes: Redundancy in planning, outdoor classrooms, workable PPE plans, cohorting/pods
  - Controlled community rates **critical** for safe re-opening



NYT. 2020. When COVID subsided, Israel Re-Opened Its Schools. It Didn't Go Well.

Science. 2020. School Openings Across the Globe Suggest Ways to Keep Coronavirus at Bay.

European CDC Report. Available at:

<https://www.ecdc.europa.eu/sites/default/files/documents/COVID-19-schools-transmission-August%202020.pdf>

60



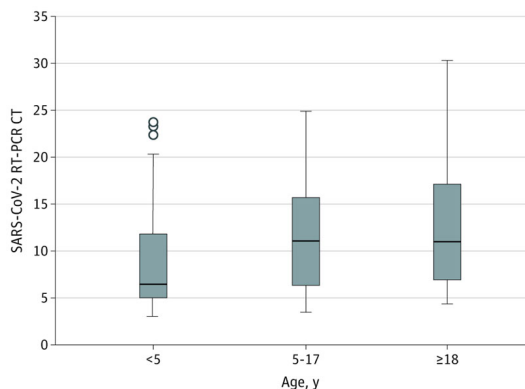
## School Re-Opening Successes

Country/ State	Infection Control Interventions	Summary/Key Findings
England	<ul style="list-style-type: none"> <li>2 meters at all times between adults</li> <li>Maintain distancing "if possible" between children</li> <li>Classes in bubbles, hand hygiene</li> </ul> <small>www.gov.uk/government/publications/actions-for-schools-during-the-coronavirus-outbreak/guidance-for-full-opening-schools</small>	<ul style="list-style-type: none"> <li>&gt;20,000 schools, &gt;1 million children</li> <li>67 single cases, 30 clusters, most transmissions staff → staff or staff → student</li> <li>Outbreaks correlated with community prevalence and index cases tied to community transmissions</li> </ul> <small>www.gov.uk/government/publications/sars-cov-2-infection-and-transmission-in-educational-settings</small>
Rhode Island	<ul style="list-style-type: none"> <li>Cohorting</li> <li>Universal masking for adults only</li> <li>Daily symptom screen for adults and children</li> <li>Enhanced cleaning</li> </ul>	<ul style="list-style-type: none"> <li>Childcare centers with capacity of 19,000 children</li> <li>Confirmed cases: 30 children, 22 adults</li> <li>20/29 of the centers with a positive case had 0 secondary transmissions, and 2/29 with 2-5 cases, but these were traced to other sources</li> </ul> <small>www.cdc.gov/mmwr/volumes/69/wr/mm6934e2.htm#F1_down</small>
Australia	<ul style="list-style-type: none"> <li>Reduced class size</li> <li>Contact tracing</li> <li>Given the study period, not all interventions implemented for the entire study (1/25-4/9, schools encouraged distance learning after 3/22).</li> </ul>	<ul style="list-style-type: none"> <li>Estimated 143,084 school staff, 1,232,367 students</li> <li>27 index cases (15 children, 12 adults)</li> <li>18 secondary cases (1.2% attack rate)               <ul style="list-style-type: none"> <li>Child to child transmission rate: 0.3%, staff to child transmission rate: 1.5%, child to staff transmission rate: 1%, staff to staff transmission rate: 4.4%</li> </ul> </li> </ul> <small>www.thelancet.com/journals/lanchi/article/PIIS2352-4642(20)30251-0/fulltext</small>
Ireland	<ul style="list-style-type: none"> <li>Evaluated transmissions related to schools prior to closure</li> </ul>	<ul style="list-style-type: none"> <li>3 pediatric cases and 3 adult cases identified</li> <li>0 with epidemiologic links to transmission in schools (travel/community transmissions)</li> </ul> <small>www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.21.20009038html_fulltext</small>
Singapore	<ul style="list-style-type: none"> <li>Infection control measures: daily symptom screen, stay home when sick policy, hand hygiene, cohorting, "safe distancing," defined as 1 meter apart, masking policy</li> <li>Close contacts quarantined, non-close contacts attend school</li> <li>Terminal cleaning</li> <li>Measures to reduce student mixing (e.g., extracurriculars cancelled and staggered recess breaks)</li> </ul> <small>www.moe.gov.sg/faqs-covid-19-infection</small>	<ul style="list-style-type: none"> <li>3 positive cases with contact tracing, no secondary cases</li> </ul> <small>academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa794/5862649</small>

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## Can Kids Spread COVID-19?

### Single Center Study: Pediatric Shedding (Tertiary Care Pediatrics Hospital)



Head-Sargent et al. JAMA Pediatrics. 2020

### Contact Tracing after Index Pediatric Case in South Korea

- 107 index cases in pediatric patients
- Evaluated 248 secondary household contacts (social distancing attempted)
- 1 transmission (secondary attack rate, 0.5%, range 0-2.6%)

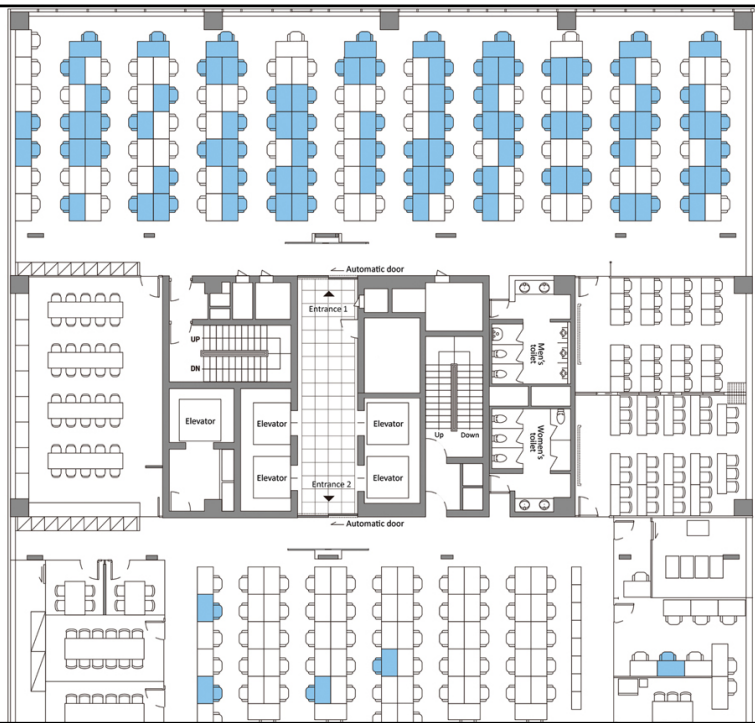
Kim et al. Archives of Disease in Childhood. August 11, 2020: <https://adc.bmj.com/content/early/2020/08/06/archdischild-2020-319910?s=03>

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## Telephone Center

- Call Center in South Korea
- Outbreak February, 2020
- 1143 tested
- 97 positive
  - Blue seats indicate positive cases
  - 43.5% on one floor
- 16.2% secondary (household) attack rate

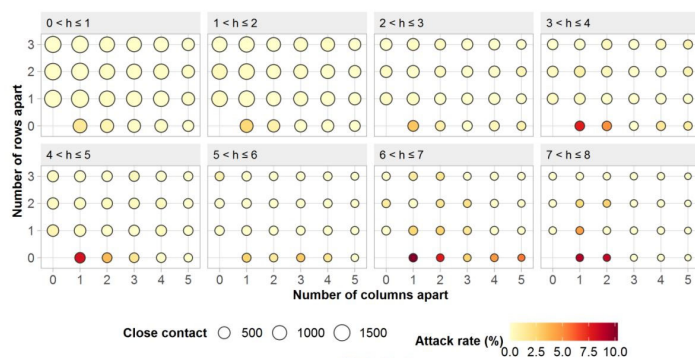
*Park et al. Emerging Infectious Diseases. 2020*



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## COVID spread on a train

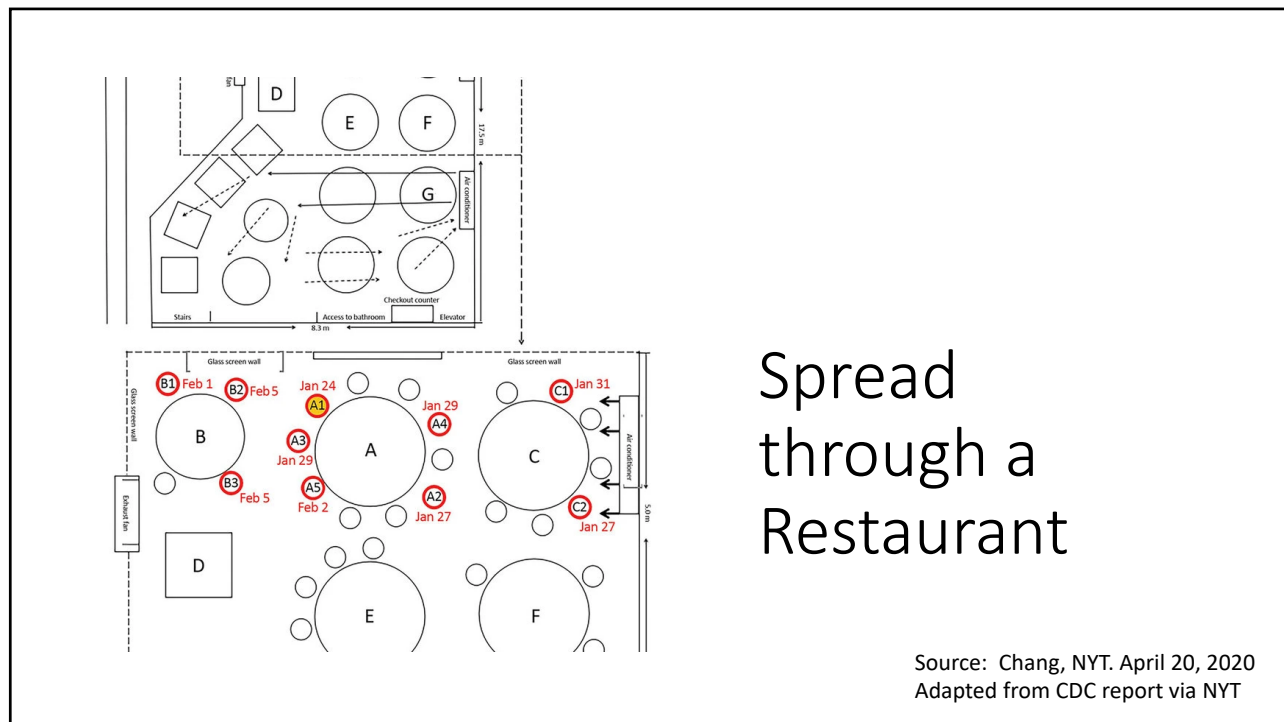
- Cohort study of train riders: 2,334 index patients and 72,093 close contacts who had co-travel times of 0–8 hours
- 12/2020-3/2021
- The attack rate in train passengers on seats within a distance of 3 rows and 5 columns of the index patient varied from 0 to 10.3%
  - Risk highest in the same row
  - Adjacent traveler the highest risk (3.5%)
  - Risk increased with increased travel time (0.15% per hour)
  - Decreased rapidly with distance



*Hu et al. Clinical Infectious Diseases. 2020*

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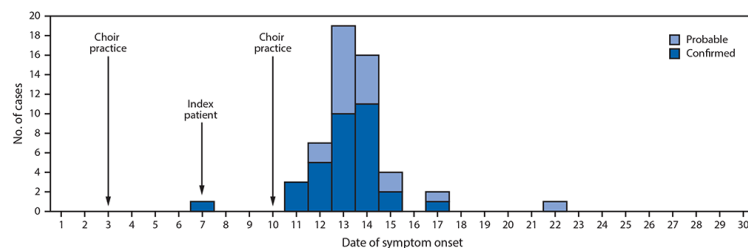
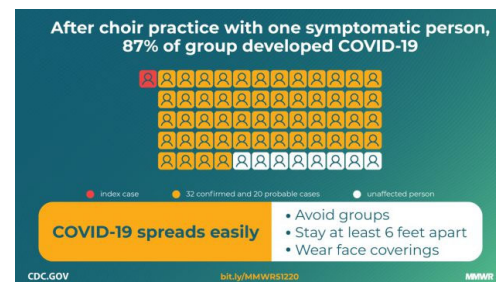




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## The CHOIR Case: Superspreading event

- 61 attendees, 32 confirmed and 20 probable secondary infections
- 2.5 hour long practice
  - Members sitting close together (chairs 6-10 inches apart)
  - Shared food/snacks
  - Close contacts (stacking chairs/interactions)
  - High-risk activities (singing)

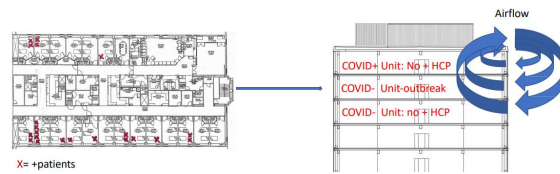


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## Hospital-Based Outbreak: Bay State Medical Center

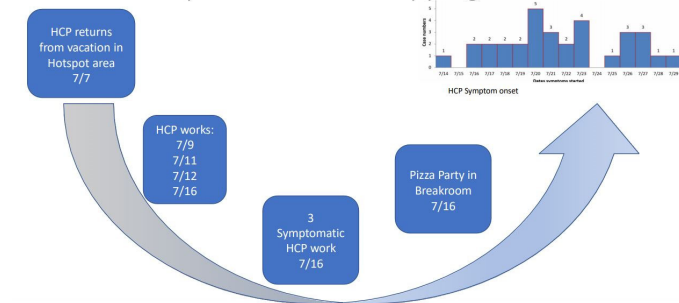
- 36 HCW and 22 patients infected during a two-week window
- Cluster investigation found:
  - Presenteeism
  - Distancing not followed
  - Mask non-adherence
  - Masks worn incorrectly
- Cluster controlled with simple measures (not change to ventilation system):
  - Mask education
  - Distancing enforced
  - New break room areas with larger spaces identified
  - Pre-screening/quarantining rules
  - Enhanced cleaning of patient rooms

Could This have been Airborne Spread?



ANSWER: NO

Preliminary transmission mapping

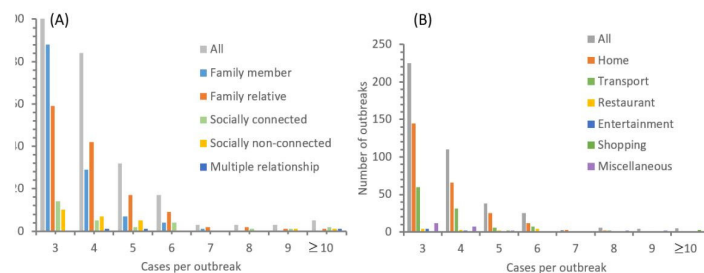


Slide adapted from SHEA Town Hall and courtesy of Sarah Haessler.

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## Indoor versus Outdoor Transmission

- 318 independent clusters (defined as three or more cases)
- 1245 confirmed cases in 120 cities
- Home environments the dominant category (254/318 clusters)
- Transport second highest risk (108)
- Only 1 cluster occurred in an outdoor environment (and included only two cases)



Qian et al. Indoor Transmission of SARS-CoV-2. Pre-print

68

## Case Study: Georgia Camp

- 597 Georgia residents attended the camp
- 344 with available test results
- 260 positive tests/597 total (not everyone was tested, confirmed attack rate 44%)
  - Children and staff both infected
  - Unclear whether campers or staff drove the outbreak
- Measures not taken:
  - No masks for campers
  - Opening of windows/ventilation recommendations not followed
  - Indoor and outdoor activities, including high-risk activities, such as “vigorous” singing and cheering

Szablewski CM, Chang KT, Brown MM, et al. SARS-CoV-2 Transmission and Infection Among Attendees of an Overnight Camp — Georgia, June 2020. MMWR Morb Mortal Wkly Rep. ePub: 31 July 2020.  
DOI: <http://dx.doi.org/10.15585/mmwr.mm6931e1external icon>.

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## Where does the evidence for 6-feet of distancing come from?

- 1897: Suggested 1-2 meters of distance based on sampled visual droplets that contained pathogens
- 1942: Still photography advanced and still images demonstrated most particles within a small range
- 1948: Study of Strep spread
  - 65% of participants with large droplet only
  - 10% with spread up to 2.9 meters (9.5 feet) away
- 2020:
  - UK SAGE: Risk of transmission at 1 meter 2-10X higher than at  $\geq 2$  meters
  - WHO Systematic Review (mostly from SARS-CoV-1, MERS) Estimates:  $<1$  meter: Risk of transmission  $\sim 12.5\%$ , versus  $\sim 2.6\%$  at distances  $\geq 1$  meter

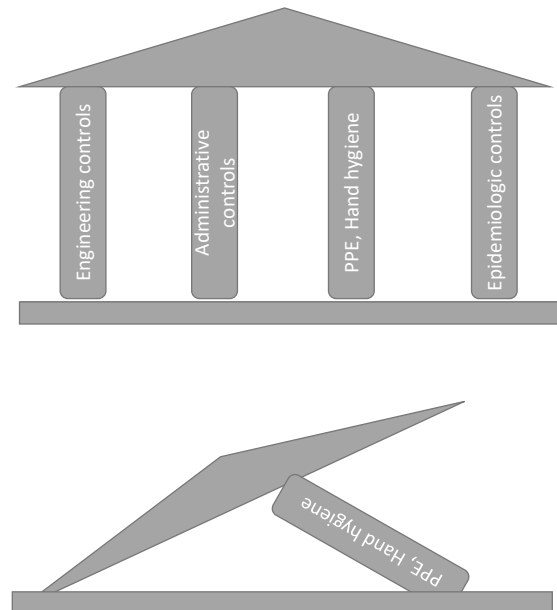


Jones et al, BMJ. 2020. Two metres or one: what is the evidence for physical distancing for COVID? Photo reprinted from Jennison, 1942.

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## Take Home II

- Develop infection control plans assuming that *anyone* can become infected and *anyone* can spread the infection
- We can leverage what we know about linking mode of transmission to infection control strategy
  - These include engineering, administrative, epidemiologic, and PPE/hand hygiene controls
- None of these strategies is fool-proof, so always rely on more than one
  - A temple can stand with four columns, and maybe even two, but certainly not one!
- Make sure your plan is one that is acceptable, feasible, and sustainable



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## Take Home Points

- COVID-19 primarily spreads via small and large droplets and contact with mucus membranes
  - This likely includes ocular transmission, although still a source of debate
  - Masking key to controlling spread
- Contact-based transmission is not a predominant mode of spread, but don't forget the basics: good hand hygiene always important
- Mass vaccination a key infection control strategy, but is not critical for re-opening schools safely
  - Open questions about the effectiveness of vaccination in children and realistic timeframe for vaccinating children

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## This is Medical Grand Rounds. Why Are We Talking about Elementary and Secondary Schools?

- In the US, impact 55 million students in 124,000 schools
  - 4.6 million healthcare workers with children <14
  - 30% of the total healthcare work force
- School closures estimated to cost \$13.2 -62.3 billion/month
- Healthcare system may be differentially impacted, with up to 15% reduction in capacity due to childcare challenges
- Women make up 75% of the healthcare workforce and bear the brunt of the majority of at-home learning.

***“If female healthcare workers are forced to keep juggling tutoring and their jobs, the medical system may not hold. And we need it to hold.”***

Chavi Karkowsky, writing for the Washington Post. July 24, 2020.

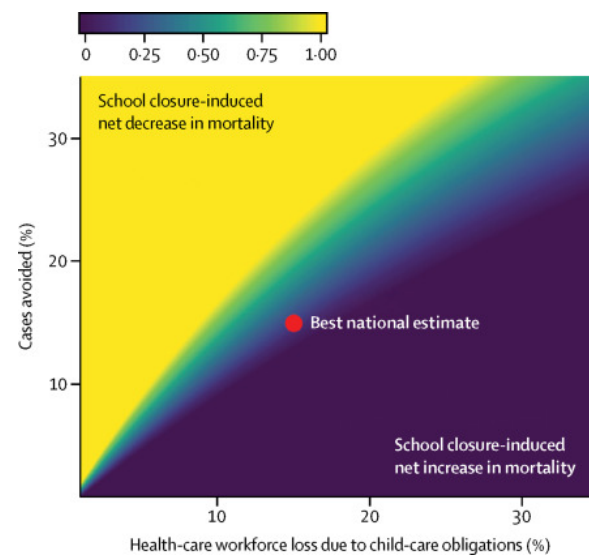
Lempel. Economic Cost and Healthcare Worker Effects of School Closure in the US. Plus Current, 2009.

Karkowsky. The Child-Care Crisis Punishes Women in Healthcare. Without Schools, They'll Quit. Washington Post, July 2020.

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## Childcare Crisis: Impact on Healthcare

- US Population survey:
  - 3.1 million individuals in 1.3 million households
  - US healthcare sector with among the highest childcare needs
    - 28.8% of the US healthcare work force caring for children aged 3-12
    - 6.8% in single-parent homes
  - Assume:
    - 15% decrease in case load
    - At 15% decrease in HCW labor force, 17.6% increase in mortality
  - Model: 15% reduction in HCW increased mortality from 2.0% → 2.3%



Beyham. The Lancet Public Health. May 2020.

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## Survey of MGH/Brigham Network (Largest in MA)

### 6,000 Respondents across the Network

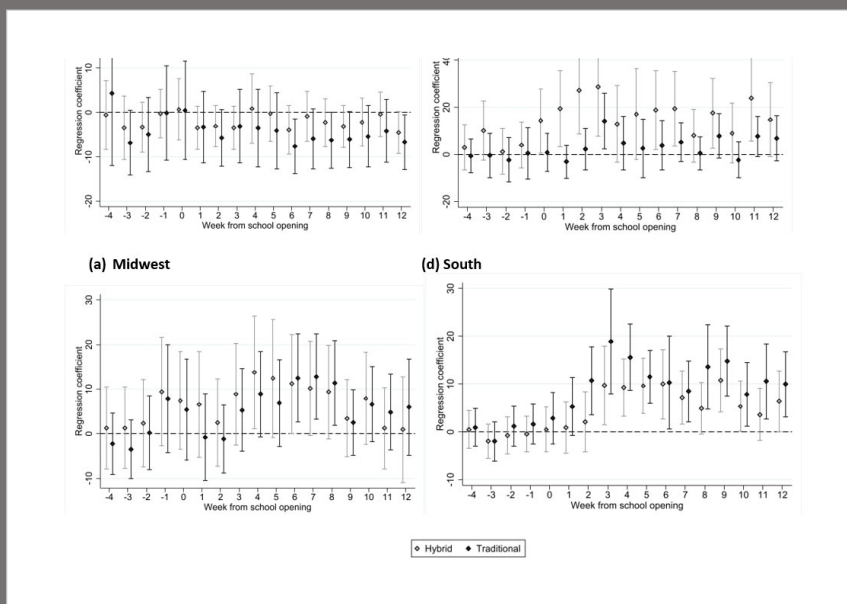
- 50% considering re-arranging their work schedule
- 35% considering working fewer hours
- 25% considering a leave of absence
- 20% considering quitting to supervise children at home

### Supports offered by MGH/Brigham

- Day care and nanny discounts
- Six daycare centers
- Access to tutoring assistance and help creating learning pods

Remote Learning Strains Medical Workers and their Employers. WBUR Commonwealth. Sept 8, 2020. Martha Bebinger

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What is the Impact of Schools on Cases in the Community?

Ertem et al. Under Review. 2021. <https://www.researchsquare.com/article/rs-712725/v1>

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