

1. Risk Factors for severe COVID-19:

a. Infection Fatality Rate is extremely age dependent

Ioannidis JPA. Infection fatality rate of COVID-19 inferred from seroprevalence data. *Bull World Health Organ.* (2021a) 99:19-33F.

Levin AT, Hanage WP, Owusu-Boaitey N, Cochran KB, Walsh SP, Meyerowitz-Katz G. Assessing the age specificity of infection fatality rates for COVID-19: systematic review, meta-analysis, and public policy implications. *Eur J Epidemiol.* (2020) 35:1123-1138.

O'Driscoll M, Dos Santos GR, Wang L, Cummings DAT, Azman AS, Paireau J, et al. Age-specific mortality and immunity patterns of SARS-CoV-2. *Nature* (2021) 590:140-145.

Ioannidis JPA. Reconciling estimates of global spread and infection fatality rates of COVID-19: an overview of systematic evaluations. *Eur J Clin Invest.* (2021b) 51:e13554.

Axfors C, Ioannidis JPA. Infection fatality rate of COVID-19 in community-dwelling populations with emphasis on the elderly: An overview. Version 2. medRxiv 2021.

<https://doi.org/10.1101/2021.07.08.21260210> .

-The proportion of location's total COVID-19 deaths among elderly median 86% (range 51-93%) in HIC; proportion in nursing home residents median 43% (range 20-85%) in HIC. The IFR community dwelling elderly (age 70y+) median 2.9% (range 0.2-6.9%), and assuming a conservative 5% relative monthly sero-reversion, IFR in community dwelling elderly 2.4% (range 0.2-5.9%). The IFR by age was: 0-19y IFR 0.0013% (1/76,900); 20-29y IFR 0.0088% (1/11,300); 30-39y IFR 0.021% (1/4,800); 40-49y IFR 0.042% (1/2,400); 50-59y IFR 0.14% (1/714); 60-69y IFR 0.65% (1/154).

Joffe AR, Redman D. The SARS-CoV-2 pandemic in high income countries such as Canada: A better way forward without lockdowns. 2021 OSF Preprints. <https://doi.org/10.31219/osf.io/r8d6f> . Now in press at:

<https://www.frontiersin.org/articles/10.3389/fpubh.2021.715904/abstract>

-see Tables 1 and 2 that summarize the above IFR references, and compare them to Influenza deaths in 2019 in the USA

Sen P, Yamana TK, Kandula S, Galanti M, Shaman J. Burden and characteristics of COVID-19 in the United States during 2020. *Nature* 2021;598:338-341.

-modeled that the national population-weighted ascertainment rate averaged for all of 2020 was 21.8% (15.9, 30.3), and the national IFR during the latter half of 2020 hovers around 0.30%.

Smith C, Odd D, Harwood R, Ward J, Linney , Clark M, et al. Deaths in children and young people in England after SARS-CoV-2 infection during the first pandemic year. *Nature Medicine* 2021.

<https://doi.org/10.1038/s41591-021-01578-1>.

-In children age <18y from Mar/20 to Feb/21 in England, of 3105 deaths overall [including 124 from suicide and 268 from trauma], 61 tested positive for SARS-CoV-2, of whom 25 (41%) were determined to have died of SARS-CoV-2 [0.8% of all deaths]. The survival from SARS-CoV-2 infection was estimated at 99.995% [IFR 0.005%]. Risk factors included age 10-17y, Asian or black ethnicity, and comorbidities; but the absolute risk in each risk group was extremely low, accounting for <3% of their deaths overall. Most SARS-CoV-2 deaths had a life-limiting condition (60%), 2+ comorbidities (64%), and/or complex neuro-disability (52%), and none had isolated respiratory (CF, asthma), diabetes, Down's syndrome, epilepsy, or mental health disorder, or were a neonate.

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Kinszer K, McKinnon B, Bourque N, Pierce L, Saucier A, Otis A, et al. Seroprevalence of SARS-CoV-2 antibodies among children in school and day care in Montreal, Canada. JAMA Netw Open 2021;4(11):e2135975.

-in 4 neighborhoods of Montreal, in children aged 2-17yo, seroprevalence Mar-Apr/21 was 8.4% (4.4, 12.4), of whom 78 (82%) were not tested or tested negative with PCR (and 9 who were PCR positive in past who had negative serology). All mild 52% or no (48%) symptoms. More likely in racial/ethnic minority groups (adjusted ratio 1.9 (1.1, 2.8). No preventive practices were associated with the serological status of children. Thus, infection adverse events rates will be at least 5X lower than case adverse event rates.

b. Other important risk factors include physical inactivity, obesity, and poor diet.

Sallis R, Young DR, Tartof SY, Sallis JF, Sall J, Li Q, Smith GN, Cohen DA. Physical inactivity is associated with a higher risk of severe COVID-19 outcomes: a study in 48 440 adult patients. Br J Sports Med 2021. <https://doi.org/10.1136/bjsports-2021-104080>.

-Being inactive (0-10min/wk) was associated with higher hospitalization OR 2.26 (1.81, 2.83), ICU admission OR 1.73 (1.18, 2.55), and death OR 2.49 (1.33, 4.67) compared to meeting activity guidelines (150+min/week). Being inactive was associated with higher hospitalization OR 1.20 (1.10, 1.32), ICU admission OR 1.10 (0.93, 1.29), and death OR 1.32 (1.09, 1.60) compared to having some physical activity (11-149min/week). The increased risk exceeded the odds of smoking and virtually all the chronic diseases studied [except for age and a history of organ transplant]. The authors concluded that regular physical activity may be the single most important action individuals can take to prevent severe COVID-19 and its complications.

Merino J, Joshi AD, Nguyen LH, Leeming ER, Mazidi M, Drew DA, et al. Diet quality and risk and severity of COVID-19: a prospective cohort study. Gut 2021. doi: 10.1136/gutjnl-2021-325353

-A pre-pandemic healthful Plant-Based Diet reduced risk of COVID-19: low-quality vs high-quality diet reduced the risk of symptomatic COVID-19 aHR 0.91 (0.88, 0.94); for severe COVID-19 aHR 0.59 (0.47, 0.74). The authors suggested we “should consider specific attention to improve nutrition as a social determinant of health.”

Kim H, Rebholz CM, Hegde S, LaFiura C, Raghavan M, Lloyd JF, et al. Plant-based diets, pescatarian diets and COVID-19 severity: a population-based case-control study in six countries. BMJ Nutrition Prevention & Health 2021 <https://doi.org/10.1136/bmjnph-2021-000272>.

-plant-based diets had lower risk, OR 0.27 (95% CI 0.10, 0.81), of moderate-to-severe COVID-19, adjusted for age, sex, race/ethnicity, country, medical specialty, smoking, physical activity, BMI, and medical condition.

Kompaniyets L, Goodman AB, Belay B, Freedman DS, Sucusky MS, Lange SJ, et al. Body mass index and risk for COVID-19-related hospitalization, intensive care unit admission, invasive mechanical ventilation, and death – United States, March-December 2020. MMWR 2021;70.

-risks for hospitalization, ICU, and death were lowest at BMI 24.2, 25.9, 23.7 respectively, and then increased sharply with higher BMIs. Risk for invasive ventilation in ICU increased over the full range of BMIs. The authors concluded that this suggests the need to promote and ensure community access to nutrition and physical activity opportunities that promote and support a healthy BMI.

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Gao M, Piernas C, Astbury NM, Hippisley-Cox J, O’Rahilly S, Aveyard P, Jebb SA. Associations between body-mass index and COVID-19 severity in 6.9 million people in England: a prospective, community-based, cohort study. Lancet Diabetes Endocrinol 2021.

-at a BMI of >23 kg/M² there was a linear increase in risk of severe-COVID-19 leading to admission to hospital and death, and a linear increase in admission to an ICU across the whole BMI range.

c. Teachers (and students) are not at higher risk:

Gandini S, Rainisio M, Iannuzzo ML, Bellerba F, Cecconi F, Scorrano L. A cross-sectional and prospective cohort study of the role of schools in the SARS-CoV-2 second wave in Italy. Lancet Regional Health – Europe 2021;5:100092.

-incidence among students was lower than in the general population; secondary infections at school were <1%, and clusters of ≥2 secondary cases occurred in 5-7% of analyzed schools. Incidence among teachers was comparable to the population of similar age (p=0.23); secondary infections among teachers were rare, occurring more frequently when the index case was a teacher than a student (37% vs. 10%, p=0.007). School closures in 2 regions where they were implemented before other measures did not affect transmission decrease.

Somekh I, Boker LK, Shohat T, Pettoello-Mantovani M, Simoes EF, Somekh E. Comparison of COVID-19 incidence rates before and after school reopening in Israel. JAMA Netw Open 2021;4(4):e217105.

-children aged 0-9 had the lowest increases in incidence rates and in positivity relative risks during the 2 school attendance time periods.

Fenton L, Gribben C, Caldwell D, Colville S, Bishop J, Reid M, White J, et al. Risk of hospital admission with covid-19 among teachers compared with healthcare workers and other adults of working age in Scotland, March 2020 to July 2021: population based case-control study. BMJ 2021;374:n2060

-in Scotland, teachers showed lower risk of hospital admission with covid-19 RR 0.77 (0.64, 0.92) and of severe covid-19 0.56 (0.33, 0.97) than the general population. The corresponding findings for household members of teachers were 0.91 (0.67, 1.23) and 0.73 (0.37, 1.44), showing lack of increased risk.

Bark D, Dhillon N, St-Jean M, Kinniburgh B, McKee G, Choi A. SARS-CoV-2 transmission in K-12 schools in the Vancouver Coastal Health Region: a descriptive epidemiologic study. CMAJ Open 2021;9(3): <https://doi.org/10.9778/cmajo.20210106>

-in 26 clusters with school-based transmission: 55 secondary cases, which is 55/123,646 (0.04%) of those in school and in 25/378 (7.0%) of schools; ratio of secondary cases to total primary cases was 0.09 in the school setting. The authors concluded that “In-person school attendance may not expose students and staff to higher risks than those experienced in the community.”

Goldfarb DM, Masse LC, Watts AW, Hutchison SM, Muttucomaroe L, Bosman ES, et al. SARS-CoV-2 seroprevalence among Vancouver public school staff in British Columbia, Canada. medRxiv 2021 <https://doi.org/10.1101/2021.06.16.21258861>

-incidence of COVID-19 cases among students attending in-person was 9.8/1000 during 2020/21 school year, among staff 13/1000 since beginning of pandemic; only 1.4% (24/1688) of staff reported a positive test. The adjusted seroprevalence in staff who gave blood was 2.3% (1.6, 3.2) compared to 2.3% (1.7, 3.0) in blood donors, suggesting no detectable increase in seroprevalence among school staff above the community seroprevalence.

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Ciaranello A, Bell T. Using data and modeling to understand the risks of in-person education. JAMA Netw Open 2021;4(3):e214619

-Studies have generally demonstrated similar or lower risks among children and adults who have been present in school buildings, compared with general population rates, and student-to-staff transmission has been rare [most adult infections have been acquired from other adults, often when unmasked while eating or drinking]. US and European studies have shown equivocal results about the association of school closure or opening with COVID-19 incidence, hospitalization, and deaths in the community.

Fukumoto K, McClean CT, Nakagawa K. No causal effect of school closure in Japan on the spread of COVID-19 in spring 2020. Nature Medicine 2021. <https://doi.org/10.1038/s41591-021--1571-8>.

-Matching each municipality with open schools to a municipality with closed schools that is the most similar in terms of potential confounders “we did not find any evidence that school closures in Japan reduced the spread of COVID-19.”

Ladhani SN, the sKIDs Investigation Team. Children and COVID-19 in schools. The benefits of in-person schooling with mitigations in place outweigh risks of COVID-19 for children. Science 2021;374(6568):680-682.

-Makes several points. First, school closure harms children [with effects on education, social and emotional well-being, welfare services, school meals, school-based immunization]. Second, children almost invariably developed mild, transient, and self-limiting illnesses – case fatality rates are strongly associated with age. Third evidence suggests that school opening is not harmful. In the UK there were very few infections and outbreaks during the 6wk [of reopening] until mid-July/20, with most cases affecting staff and limited transmission among students [4/603 (0.7%) of 4-12yo students and 1/1015 (0.1%) of staff seroconverted; when outbreaks occurred, more than half involved only 2 cases]; antibody positivity rates were similar in students and staff and comparable to local community seroprevalence. IN the US, several active contact tracing studies found that very low rates of secondary infections occurred inside educational premises in K-12 [e.g., in North Carolina surveillance of 11 districts with >90K students and staff over 9 weeks found 773 community-acquired and 32 school-acquired infections; in Wisconsin incidence among students and staff in Sept-Nov was lower than in the county overall, and only 7/191 (3.7%) cases in students and staff were linked to in-school spread; in New York City prevalence in public schools was similar or less than community prevalence Oct-Dec/20, and only 191/36423 (0.5%) close school-contacts tested positive.

Etrem Z, Schechter-Perkins EM, Oster E, van den Berg P, Epshtein I, Chaiyakunapruk N, et al. The impact of school opening model on SARS-CoV-2 community incidence and mortality. Nature Medicine 2021. <https://doi.org/10.1038/s41591-012--01563-8>.

-During the 12 weeks after school opening (July-Sept/20), SARS-CoV-2 incidence rates were not statistically different in counties with in-person learning versus remote school modes in most regions of the United States, and there was no impact of school opening mode on subsequent COVID-19-related deaths in any region. In the “South, there was a significant and sustained increase in cases per week among counties that opened in a hybrid or traditional mode versus remote, with weekly effects ranging from 9.8 (2.7, 16.1) to 21.3 (9.9, 32.7) additional cases per 100K persons.” The authors “suggest that schools can open for in-person learning during the pandemic with minimal contribution to sustained community incidence of infections.”

Walsh S, Chowdhury A, Braithwaite V, Russell S, Birch JM, Ward JL, et al. Do school closures and school reopenings affect community transmission of COVID-19? A systematic review of observational studies. BMJ Open 2021;11:e053371.

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-A review of 40 studies up to 7Jan/21 from 150 countries. In school closure studies, there was substantial heterogeneity, with half of studies at lower risk of bias reporting reduced community transmission and half reporting null findings. Studies were confounded by other NPIs implement around same time. Authors concluded that the effectiveness of school closures remains uncertain. In school reopening studies, 3 out of 4 studies at lower risk of bias reported no associated increases in transmission.

Halloran C, Jack R, Okun JC, Oster E. Pandemic schooling mode and student test scores: evidence from US states. NBER working paper series. Working Paper 29497. <http://www.nber.org/papers/w29497>.

-across 12 states, pass rates declined compared to prior years and these declines were larger in districts with less in-person instruction.

Wood R, Thomson E, Galbraith R, Bribben C, Caldwell D, Bishop J, et al. Sharing a household with children and risk of COVID-19: a study of over 300 000 adults living in healthcare worker households in Scotland. Arch Dis Child 2021;106:1212-1217.

-After schools reopened to all children 12 Aug/20, with active transmission of SARS-CoV-2 in the community, up until 12 Oct/20, there was no association seen between exposure to young children and risk of any COVID-19 (aHR per child in household 1.03; 95% CI 0.92, 1.14).

Forbes H, Morton CE, Bacon S, McDonald HI, Minassian C, Brown JP, et al. Association between living with children and outcomes from covid-19: OpenSAFELY cohort study of 12 million adults in England. BMJ 2021;372:n628.

-wave 1 (1Feb-31Aug/20) and wave 2 (1Sept-18Dec/20) risk for covid (clinical or swab diagnosis) in adults 18yo+ in adjusted models

Wave	Age group	Risk from living with children in the household				
		Infection	Hospitalization	ICU admission	COVID-19 death	Non-COVID-19 death
1	≤65y	None	None	None	None	HR 0.61 (0.54, 0.69)
1	>65y	None	None	None	None	None
2	≤65y	HR 1.25 (1.23, 1.27)	HR 1.44 (1.28, 1.63)	None	None	HR 0.77 (0.64, 0.91)
	Child 0-11y Child 12-18y	0.4-0.6/100 1.6-1.9/100	0.01-0.05/100 0.02-0.06/100		HR 0.52 (0.35, 0.78)	
2	>65y	HR 1.27 (1.14, 1.42)	None	HR 1.86 (1.11, 3.14)	HR 1.44 (1.05, 1.97)	None

-absolute increases in risks of infection and hospital admission among adults living with children in wave 2 were small, and did not translate into a materially increased risk of covid-19 mortality

Kazemi P, Hoeg TB, Grant J, Fulford M. Opinion: Time for kids to get back to normal. National Post. Nov 26, 2021.

-Discusses that, despite the accumulation of massive amounts of reassuring scientific data, the public continues to worry that COVID-19 poses a risk to children. The data finds that most children are asymptomatic; hospitalization rates are overestimated at 0.1-0.5%; mortality is very rare [for 5-14yo in the US, MVC and suicide are each responsible for 10X and 7X the number of deaths than from COVID-19, and the number of deaths since Jan/20 attributed to COVID-19 was less than the number of youth

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influenza deaths in the 2017/18 and 2018/19 seasons combined]; and long-COVID is rare. In addition, that schools do not play a major role in viral spread; and teachers are not at higher risk from COVID-19 than those working in other professions. All this despite the immense adverse effects on children of school closures.

Golden A, Fulford M. The wrong people are making decisions on school closures. Our children deserve better. We cannot continue to let external bodies without expertise in children's health influence these decisions. Closures are hurting our kids. National Post. Jan 11, 2022.

-“Ontarians have been convinced that there is scientific justification for school closures... [but data] tell us quite the opposite”. This data includes: “Omicron is at least 50% less virulent than prior variants”, children “seldom become seriously ill”, “persistent symptoms following COVID-19 infection are comparable to that of other common viral illnesses”, “schools have never been shown to be amplifiers of transmission and instead mirror what is happening in communities”, “school-acquired cases [only] representing approximately 1.0% of individuals working in or attending schools”, “teachers are at no higher risk of severe outcomes from COVID-19”, and “teachers at lower risk than age-matched workers”. Moreover, children “have suffered immensely from ongoing school closures and these harms will have long-lasting effects... it is time to stand up and say enough is enough. Our children deserve better... until Ontarians stand together in support of our most vulnerable, school closures will continue to be imposed at the expense of the well-being of children and families.”

2. The risk of long-COVID:

a. Long-COVID is rare in children

Buonsenso D, Munblit D, De Rose C, Sinatti D, Ricchiuto A, Carfi A, Lantini P. Preliminary evidence on long COVID in children. Acta Paediatrica 2021 <https://doi.org/10.1111/apa.15870>.

-at 162.5 (113.7) days after COVID diagnosis, 41.8% completely recovered, 35.7% had 1-2 symptoms, and 22.5% had 3 or more symptoms [which, correcting for the MIS-C incidence of 2.3% in their cases but <1/3000 in SARS-CoV-2 infections, means <1/300 had 3 or more symptoms]. Fatigue was the symptom in 10.8% [but fatigue “more – compared to before COVID-19 diagnosis” occurred in only 1 (0.8%)].

Molteni E, Sudre CH, Canas LS, Bhopal SS, Hughes RC, Antonelli M, et al. Illness duration and symptom profile in a large cohort of symptomatic UK school-aged children tested for SARS-CoV-2. Lancet 2021. [https://doi.org/10.1016/S2352-4642\(21\)00198-X](https://doi.org/10.1016/S2352-4642(21)00198-X)

-77/1734 (4.4%; 95% CI 3.5, 5.5) illness duration ≥28d vs. 0.9% (0.5, 1.4) in matched cohort, but did not involve attentional problems, memory complaints, or anxiety. 25/1379 (1.8%; 95% CI 1.2, 2.7) illness duration ≥56d, and symptom burden did not increase with time. However, normative data outside of the pandemic suggest prevalence and persistence of symptoms in general pediatric population are common: ~60% are ‘prone to headache’; 66% had headaches over the previous year; 4.4% had ‘more than a few days of disabling fatigue’; ‘fatigue lasting over 6mo associated with absence from full-time school or that had prevented participation in activities’ 1.5% at age 13y and 2.2% at age 16y.

Say D, Crawford N, McNab S], Wurzel D, Steer A, Tosif S. Post-acute COVID-19 outcomes in children with mild and asymptomatic disease. Lancet Child Adolescent Health 2021;5:e22-e23.

-follow-up at 3–6mo in 151 children found 10 (6.62%) had post-acute COVID symptoms [all were symptomatic at diagnosis]; correcting for MIS-C (reported in 1.17% of their patients) this becomes 0.19% with symptoms up to 8 weeks

Radtke T, Ulyte A, Puhan MA, Kriemler S. Long-term symptoms after SARS-CoV-2 infection in children and adolescents. JAMA 2021

-found that 9.2% seropositive vs. 9.7% seronegative had at least 1 symptom beyond 4wk, and 3.7% seropositive vs 2.2% seronegative had at least 1 symptom beyond 12wk [no difference]. A similar proportions of seropositive and seronegative children reported excellent or good health (94% vs 96%)

Blankenburg J, Wekenborg MK, Reichert J, Kirsten C, Kahre E, Haag L, et al. Mental health of adolescents in the pandemic: Long-COVID-19 or Long-Pandemic Syndrome? medRxiv 2021.

<https://doi.org/10.1101/2021.05.11.21257037>.

-in Grade 8-12 students each symptom was present in at least 35% of the students within the last 7d, with no difference comparing seropositive to seronegative students; self-reported mental distress also did not differ. The authors suggest that this confirms the negative effects of lockdown measures

Zimmermann P, Pittet LF, Curtis N. How common is long COVID in children and adolescents? PIDJ 2021

-14 studies with major limitations and marked heterogeneity; 5 studies included controls and 2 did not find persistent symptoms to be more prevalent in children and adolescents with evidence of SARS-CoV-2 infection [symptoms are difficult to distinguish from pandemic-associated symptoms due to lockdown]. The authors “suggest that infection-associated symptoms are not necessarily more common or severe than pandemic-associated symptoms.” Many of the over 200 symptoms attributed to long-COVID are nonspecific and highly prevalent in the general population.

Zavala M, Ireland G, Amin-Chowdhury Z, Ramsay ME, Ladhani SN. Acute and persistent symptoms in children with PCR-confirmed SARS-CoV-2 infection compared to test-negative children in England: active, prospective, national surveillance. Clin Infect Dis 2021. <https://doi.org/10.1093/cid/ciab991>.
-in children age 2-16y those experiencing ongoing symptoms at least 5X/month at least 1 months after a PCR+ test (compared to PCR- controls) were 21/320 (6.73%) symptomatic Covid-19 cases vs 6/154 (4.20%) symptomatic controls experienced ongoing symptoms (p=0.24).

The toll on mental health in children (the contemporary controls without long-COVID during the pandemic) has been very high

Racine N, McArthur BA, Cooke JE, Elrich R, Zhu J, Madigan S. Global prevalence of depressive and anxiety symptoms in children and adolescents during COVID-19. A Meta-analysis. JAMA Pediatr 2021;175(11):1142-1150.

-In 29 studies to Feb 16/21 including 80879 participants, the pooled prevalence of clinically elevated depressive and anxiety symptoms were 25.2% (21.2, 29.7) and 20.5% (17.2, 24.4). Prevalence was higher in studies done later in the pandemic, in girls, and for depression, in older children. This is double pre-pandemic estimates, and reflects the control group for studies of persistent symptoms in children during the pandemic.

AAP, AACAP, CHA declare national emergency in children's mental health. American Academy of Pediatrics News. 2021 Oct 19.

<https://publications.aap.org/aapnews/news/17718?autologincheck=redirected>

-discusses the escalating mental health crisis due to physical isolation, ongoing uncertainty, fear, and grief. Emergency department visits Mar-Oct/20 for mental health emergencies rose by 24% for children ages 5-11, 31% ages 12-17 in the US. Emergency Department visits for suspected suicide attempts increased nearly 51% among girls ages 12-17 in early 2021.

Viner R, Russell S, Saulle R, Croker H, Stansfield C, Packer J, et al. School closures during social lockdown and mental health, health behaviors, and well-being among children and adolescents during the first COVID-19 wave. A systematic review. JAMA Pediatr 2022. DOI: 10.1001/jamapediatrics.2021.5840.

-to Sept/20, 36 studies included, 18% to 60% of children and adolescents scored above risk threshold for distress, particularly anxiety and depressive symptoms; 3 studies suggested higher screen time usage, 2 studies reported greater social media use, and 6 studies reported lower physical activity. The authors concluded that "school closures and social lockdown during the first COVID-19 wave were associated with adverse mental health symptoms (such as distress and anxiety) and health behaviors (such as higher screen time and lower physical activity) among children and adolescents."

b. Long COVID is not common in adults

Nasserie T, Hittle M, Goodman SN. Assessment of the frequency and variety of persistent symptoms among patients with COVID-19: A systematic review. JAMA Netw Open 2021;4(5):e2111417.

-45 studies of 9751 participants reported 84 signs or symptoms and 19 laboratory or imaging measurements. Most frequent symptoms included dyspnea 36%, fatigue 40%, sleep disorders 29.4%, depression 14.9%, anxiety 22.1%, memory loss 28.3%. Frequent study quality concerns included sampling strategy being unclear or non-consecutive 14; baseline severity not reported 22; attrition not reported or at least 30% in 24 and attrition of 20-29% in 6; predominantly previously hospitalized in 16

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studies; severity of symptoms not well quantified. Studies found physical and mental health scores were mostly within 1/2 SD of population norms.

Groff D, Sun A, Ssentongo AE, Ba DM, Parsons N, Poudel GR, et al. Short-term and long-term rates of postacute sequelae of SARS-CoV-2 infection. A systematic review. JAMA Netw Open 2021;4(10):e2128568.

-57 studies reported on 38 manifestations in cases 79% of whom were hospitalized, suggested a median 54% having at least 1 laboratory, radiologic, pathologic, or clinical sign/symptom of post-acute sequelae at 6+ months. Most common were difficulty concentrating (23.8%), generalized anxiety (29.6%), pulmonary radiologic abnormality (62.2%), general functioning impairment (44%), and fatigue or muscle weakness (37.5%). These effects were due to direct viral effects or "indirect effect on mental health due to post-traumatic stress, social isolation, and economic factors, such as loss of employment." Limitations included heterogeneity in definitions; they could not stratify incidence by severity of initial illness, comorbidities, age, or hospitalization; and, not mentioned by the authors, lack of control groups, poorly described severity of persistent symptoms, and unknown significance of laboratory and radiologic abnormalities.

Contrast these reviews with the following:

Office for National Statistics. Technical article: Updated estimates of the prevalence of post-acute symptoms among people with coronavirus (COVID-19) in the UK: 26 April 2020 to 1 August 2021.

-prevalence of any of 12 common symptoms (in last 7d) 12-16 weeks after infection 5.0% vs. 3.4% in controls [in age 2-11, 12-16, and 17-24y: 3.2% vs 4.1%, 3.0% vs 1.3%, and 3.6% vs 3.6%]. Prevalence of any of 12 continuous symptoms [need not be the same symptom at every visit] after infection for at least 12 weeks 3.0% vs 0.5% in controls [in age 2-11, 12-16, and 17-24y: 0.7%, 1.2%, and 1.5%]. Limitation is that participants may be more likely to report symptoms following a positive test because of increased awareness.

Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, et al. Attributes and predictors of long COVID. Nature Med. (2021) 27:626-631. DOI: 10.1038/s41591-021-01292-y.

-App users who had detected COVID-19 cases reported symptoms (of unknown severity) at ≥8 weeks in 4.5% and ≥12 weeks in 2.3%, of whom 43.9% had been hospitalized.

Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. Nature Medicine. (2021) 27:601-615.

-A recent review that suggested approximately 30% of hospitalized COVID-19 cases have post-acute COVID-19 syndrome (of unclear severity); this would mean that [if <5% of cases are hospitalized, then <1% of infections are hospitalized] up to 0.3% of infections end up with this syndrome.

McPeake J, Shaw M, MacTavish P, Blyth KG, Devine H, Fleming G, et al. Long-term outcomes following severe COVID-19 infection: a propensity matched cohort study. BMJ Open Res 2021;8:e001080.

-A multicenter observational cohort study of the most severe COVID-19 patients, comparing outcomes in those admitted to critical care with and without COVID-19. In 91 COVID and matched non-COVID patients, there were no significant differences in any measured outcomes [emotional, physical, and social recovery] between the two cohorts.

Whittaker HR, Gulea C, Koteci A, Kallis C, Morgan AD, Iwundu C, et al. GP consultation rates for sequelae after acute covid-19 in patients managed in the community or hospital in the UK: population based study. BMJ 2021;375:e065834.

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-Using Clinical Practice Research Datalink (CPRD) Arum [a nationally representative anonymized primary care health records covering about 23% English population, in age 18+ registered with a GP] with positive test 1Aug/20 to 14Feb/21 followed up to 9May/21, adjusted for age, sex, BMI, smoking, Charlson comorbidity index. In those who had been hospitalized: most common symptoms 4wk+ joint pain 2.7% (lower than pre-Covid), breathlessness 2.8% (a 1.4% increase), cough 1.4% (lower than pre-Covid), all others <1% (and usually <0.5%) increase from baseline (e.g., fatigue 0.81% vs 0.33%); prescriptions were for opiates 2.2% (increase less than 0.9%), paracetamol 1.8%, NSAID 1.6%. In those cared for in the Community: 8.5% had any of 27 ongoing symptom at 4wk+; most common symptoms 4wk+ joint pain 2.5% (lower than pre-Covid), abdominal pain 0.9% (from 0.8% pre-Covid), headache 0.8% (from 0.7% pre-Covid), all others <1% (and most <0.5%; e.g., fatigue 0.6% vs 0.4%; palpitations 0.3% vs 0.2%) increase from baseline; prescriptions were opioids 1.0% (slightly lower than pre-Covid), NSAID 1.2% (increase 0.05%), bronchodilators 0.8% (lower than pre-Covid). Breathlessness, headache, chest pain, and fatigue declined over time, while anxiety and depression were generally constant. Healthcare use was similar to that in the negative control group. Limitations included: possible more active monitoring of patients close to the time of diagnosis of Covid-19, and could not consider severity of any of these outcomes.

And the increasing prevalence of mental health disorders in the general population even without COVID-19 infection (i.e., the control group).

Czeisler ME, Lane RI, Wiley JF, Czeisler CA, Howard ME, Rajaratnam SMW. Follow-up survey of US adult reports of mental health, substance use, and suicidal ideation during the COVID-19 pandemic, September 2020. *JAMA Netw Open.* (2021) 4(2):e2037665.

Salari N, Hosseinian-Far A, Jalali R, Vaisi-Raygani A, Rasoulpoor S, Mohammadi M, et al. Prevalence of stress, anxiety, depression among the general population during the COVID-19 pandemic: a systematic review and meta-analysis. *Global Health.* (2021) 16:57.

-Suggest that contemporary uninfected controls during the pandemic are often experiencing social isolation, unemployment, loneliness, and ~30% prevalence of anxiety and depression.

Zaninotto P, Iob E, Demakakos P, Steptoe A. Immediate and longer-term changes in the mental health and well-being of older adults in England during the COVID-19 pandemic. *JAMA Psychiatry* 2021. DOI: 10.1001/jamapsychiatry.2021.3749.

-in older adults in England, the prevalence of clinically significant depressive symptoms increased from 12.5% before to 22.6% in June/July/20, with further rise to 28.5% in Nov/Dec/20, accompanied by increased loneliness and deterioration in QOL. Mental health and well-being continued to worsen as the COVID-19 pandemic progressed.

And the potential for nocebo effects.

Bagus P, Pena-Ramos JA, Sanchez-Bayon A. COVID-19 and the political economy of mass hysteria. *Int J Environ Res Public Health.* (2021) 18(4):1376.

-Nocebo effects due to being bombarded by reports in the press and on social media, anxiety, fear, and negative expectations can lead to at least some of the cases of prolonged symptoms.

Matta J, Wiernik E, Robineau O, Carrat F, Touvier M, Severi G, et al. Association of self-reported COVID-19 infection and SARS-CoV-2 serology test results with persistent physical symptoms among French adults during the COVID-19 pandemic. *JAMA Intern Med* 2021. In Press.

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-In 26,823 participants, having physical symptoms during the previous 4 weeks that had persisted for at least 8 weeks was associated with self-reported infection (*belief in having been infected*) with ORs ranging from 1.39 to 16.37 (e.g., fatigue OR 4.90; poor attention or concentration OR 3.42; headache OR 2.40; breathing difficulties OR 7.75; palpitations OR 5.14; chest pain OR 6.58; cough OR 4.85), and *not with having actually been infection* (i.e., serology positive, which was associated only with persistent anosmia). Thus, “symptoms may not emanate from SARS-CoV-2 infection per se,” but instead may be ascribed to SARS-CoV-2 despite having other causes.

And the general weaknesses of many long-COVID studies included in systematic reviews

Amin-Chowdhury Z, Ladhani SN. Causation or confounding: why controls are critical for characterizing long COVID. *Nature Medicine* 2021;27:1129-1130.

-Long-COVID studies have asked for self-report of up to 205 often nonspecific and prevalent persistent symptoms (that are often intermittent or relapsing or have emerged several weeks to months after infection), some of which are biologically implausible, and using cohorts with systematic selection bias (e.g., hospitalized, online recruitment, non-laboratory-confirmed diagnosis (33%)) often without appropriate matched controls (13%) (in whom 40-60% report mental-health symptoms). Conclude that “more robust, well-conducted longitudinal studies are urgently needed for proper characterization of this syndrome”.

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3. Lockdowns are based on three flawed assumptions.

Joffe AR. COVID-19: Rethinking the Lockdown Groupthink. *Front Public Health*. (2021) 9:625778.

-a cost-benefit analysis with references for many of the methods and data used

Joffe AR, Redman D. The SARS-CoV-2 pandemic in high income countries such as Canada: A better way forward without lockdowns. 2021 OSF Preprints. <https://doi.org/10.31219/osf.io/r8d6f> . Now in press at:

<https://www.frontiersin.org/articles/10.3389/fpubh.2021.715904/abstract>

-reviews 27 studies findings lockdowns are not associated with transmission of SARS-CoV-2

-reviews 11 studies finding lockdowns have higher cost than benefit in terms of population wellbeing

Joffe A, Redman D. Applying Philosophy, Logic, and Rational Argumentation to the Severe Acute Respiratory Syndrome Coronavirus-2 Pandemic Response. Preprints 2021.

<https://doi.org/10.20944/preprints202105.0264.v1>

-giving many references for the flawed lockdown assumptions

Halperin DT, Hearst N, Hodgins S, Bailey RC, Klausner JD, Jackson H, et al. Revisiting COVID-19 policies: 10 evidence-based recommendations for where to go from here. *BMC Public Health* 2021;21:2084.

-Discusses that some widely held assumptions underlying current policy approaches call for an evidence-based reassessment - maintaining a constant state of emergency is not viable. Suggest that lockdowns should be avoided “in favor of more effective, carefully targeted ‘scalpel’ public health strategies,” and that lockdowns have “far-reaching unintended consequences” [mental health, drug overdose, domestic violence, child abuse, weight gain, abuse by law enforcement, discontinuing non-COVID healthcare].

Also discusses: vaccination should be equitable, prioritize the vulnerable, and be deferred in previously infected; emphasize education and harm reduction approaches as opposed to coercive and punitive measures; keep schools open as not major drivers of transmission, and harm “dwarfs any benefits”; and de-emphasize identifying new cases [i.e., focus on mortality and hospitalization].

Alexander PE. More than 400 studies on the failure of compulsory Covid interventions. Brownstone Institute. November 30, 2021. <https://brownstone.org/articles/more-than-400-studies-on-the-failure-of-compulsory-covid-interventions/>

-reviews many studies of lockdowns, shelter-in-place policies, masks, school closures, and mask mandates that find the interventions “ineffective and devastating failures” with “no discernible impact of virus trajectories”. The benefits have been “totally exaggerated” and the harms have been “severe”. Concluding that “there is no conclusive evidence supporting claims that any of these restrictive measures worked to reduce viral transmission or deaths.” Interestingly, mentions that lockdowns didn’t protect the vulnerable but rather shifted morbidity and mortality burden to the underprivileged, and were an “assault on the working class” while protecting the “laptop affluent class.” Also cautions that “for some children, education is their only way out of poverty.”

Haber NA, Clarke-Deelder E, Feller A, Smith ER, Salomon J, MacCormack-Gelles B, et al. Problems with evidence assessment in COVID-19 health policy impact evaluation: A systematic review of study design and evidence strength. medRxiv 2021. <https://doi.org/10.1101/2021.01.21.21250243>.

-A review of the published quantitative COVID-19 policy impact on direct COVID-19 outcomes literature to 26Nov/20. Found 36 articles, and only 1 passed a set of four key design checks for identifying the causal impact of policies on COVID-19 outcomes. The literature “largely failed to meet key design criteria for inference of sufficient rigor to be actionable by policy-makers.” The main problems were in functional form [the statistical model used for the trend] and concurrent changes [other uncontrolled or unadjusted-for ways the outcome could have changed].

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And, specifically in Canada:

Vickers DM, Baral S, Mishra S, Kwong JC, Sundaram M, Katz A, et al. Stringency of containment and closures on the growth of SARS-CoV-2 in Canada prior to accelerated vaccine roll-out. (October 21, 2021). Available at SSRN: <http://dx.doi.org/10.2139/ssrn.3947387>.

-Across 5 provinces and 2 pandemic waves from 28Feb/20 to 15Feb/21, pandemic responses correlated with decreased growth of SARS-CoV-2 cases. However, this correlation attenuated as response stringency increased [steepest in first wave at average SI 25.2 out of 100 and became less negative [diminishing returns] in all subsequent SI periods], case growth declined identically regardless of a province's initial stringency [declined rapidly by 37-50% and began plateauing within the first 2 weeks of the first wave], and case growth stabilized despite incrementally stringent responses in late-2020 [no correlation with SI during second wave]. This demonstrates "a limited dose-response relationship between SI of NPIs and reduced case growth" and overall "the results of this study did not yield significant case reduction with increasing stringency of NPIs in the first and second waves across five provinces." It is likely that any early benefit rapidly saturated among those who could work from home and remain well-housed, but without effect on essential workers and those with public-facing jobs, those voluntarily avoiding busier public places, and those reallocating mobility to 'allowed' businesses. This suggests a mismatch between where the largest risk was and how restrictive NPIs were: requires targeted approaches, such as paid-leave, voluntary isolation support, and improved occupational health.

Maddeaux S. Lockdowns are killing young Canadians. National Post. Dec 30, 2021.

-just as tragic [as COVID-19 deaths] is a response [from the choices we've made along the way] that disproportionately kills the young: approximately 15.6%, or about 3100, of Canada's excess deaths [Mar/20 to May/21] occurred among those younger than 44, even though that youngest cohort accounts for only 0.7% of the country's COVID-19 deaths. These were largely due to unintentional overdoses and poisonings... younger generations are self-harming and dying in unprecedented numbers that appear to directly correlate with closures... There are lives on the other side of the scale..."

In addition, lockdowns cause risk factors for severe COVID-19 to increase

Chaffee BW, Cheng J, Couch ET, Hoeft KS, Helpert-Felsher B. Adolescents' substance use and physical activity before and during the COVID-19 pandemic. JAMA Pediatr 2021;175(7):715-722.

-Grade 9 and 10 students at 8 public high schools Northern California: being physically active declined sharply from baseline after the stay-at-home order.

Pagoto SL, Conroy DE. Revitalizing adolescent health behavior after the COVID-19 pandemic. JAMA Pediatr 2021;175(7):677-679.

-stay-at-home restrictions have had unintended implications for health-related behaviors in youth. Yet, premature decline in physical activity could track into adulthood and increase risk for chronic disease later in life [healthy and unhealthy behaviors that are established in adolescence often extend into adulthood].

Woolford SJ, Sidell M, Li X, Else V, Young DR, Resnicow K, Koebnick C. Changes in body mass index among children and adolescents during the COVID-19 pandemic. JAMA 2021

-among 5–11-year-old children, overweight or obesity increased from 36.2% to 45.7% during the pandemic (absolute increase 8.7% compared to reference period); among 12–15-year-old children there was an absolute increase of 5.2%, and among 16-17 year old an absolute increase of 3.1%.

Jarnig G, Jaunig J, van Poppel MNM. Association of COVID-19 mitigation measures with changes in cardiorespiratory fitness and body mass index among children aged 7 to 10 years in Austria. JAMA Netw Open 2021;4(8):e2121675

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-among 12 randomly selected primary schools in urban and rural districts of Klagenfurt, Australia, children with overweight or obesity increased 3.8% during the year.

Wu AJ, Aris IM, Hivert MF, Rocchio C, Cocoros NM, Klompas M, Taveras EM. Association of changes in obesity prevalence with the COVID-19 pandemic in youth in Massachusetts. JAMA Pediatrics 2021.

-among 3 practice groups across 59 sites in Massachusetts serving 1.5M socioeconomically diverse patients, prevalence of obesity pre-COVID 2018-19 vs post-COVID surgery 2019-2020 increased 1.1% (0.3, 1.9). Among boys 6-11y obesity increased overall 2.8% (0.8, 4.8), Black 6.3% (-1.0, 13.6), Hispanic 7.1% (0.1, 14.1).

And lockdowns derogate important rights

Zweig SA, Zapf AJ, Beyrer C, Guha-Sapir D, Haar RJ. Ensuring rights while protecting health: the importance of using a human rights approach in implementing public health responses to COVID-19. Health and Human Rights Journal 2021, October 25.

-the main interventions [school closures, border closures, quarantine and isolation, and limiting gatherings] exacerbated many pre-existing societal inequities and human rights violations affecting marginalized populations. Rights affected included those to: education access and quality; nutrition; work; movement; seek asylum; health and well-being; healthcare; peaceful assembly; free speech; cultural life; protection against interference with individual privacy; expression; standard of living adequate for health and wellbeing; safe shelter; protection from violence and inhumane treatment or punishment; worship and religious practice, teaching, and observance

International Commission of Jurists. The Siracusa Principles on the Limitation and Derogation Provisions in the International Covenant on Civil and Political Rights. Human Rights Quarterly 1984

-lockdowns likely did not meet the Siracusa Principles, which include: no limitation on a right... shall discriminate; only as are strictly necessary to deal with the threat to the life of the nation and are proportionate to its nature and extent... may not be imposed merely because of an apprehension of potential danger; no more restrictive means than are required for the achievement of the purpose; burden of justifying a limitation upon a right guaranteed under the Covenant lies with the state; adequate safeguards and effective remedies shall be provided by law; [state] shall be subject to controls in the exercise of their power through the parliament, courts, or other competent independent bodies; shall not be used to protect the state and its officials from public opinion or criticism; shortest time required.

Godfrey-Smith P. Covid heterodoxy in three layers. Monash Bioethics Review 2021.

<https://doi.org/10.1007/s40592-021-00140-6>.

-Discusses several important points. First, lockdown costs and benefits are not favorable, as lockdowns ignore the extreme age-dependent risk from Covid, have high costs, and have limited benefits. Second, lockdowns have resulted in many basic liberties being suppressed that are normally unthinkable to penalize, with powers gained tending not to be willingly relinquished. Third, by letting our lives be run by fear, we have ignored the nature of valuable and meaningful life experiences, resulting in intergenerational theft [loss of education, and constrained and degraded opportunities for young people during the years when they begin to shape their aspirations and find the beginning of a path into economic life and close partnerships, resulting in a loss of direction], and leaving many older people without what makes life remain valuable [loss of companionship and contact with loved ones].

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Kingsnorth P. How fear fuels the vaccine wars. Covid has been a revelation and an accelerant. UnHerd. Nov 30, 2021. <https://unherd.com/2021/11/how-fear-fuels-the-vaccine-wars/>

-Describes our “march towards authoritarianism in the name of public health.” Society has marched to “Internment. Mandatory medication. Segregation of whole sections of society. Mass sackings. A drumbeat media consensus. The systematic censoring of dissent. The deliberate creation of a climate of fear and suspicion. The deepening demonization of the ‘unvaxxed’. Something terrible is rising around us... with a scan of a smartphone-enabled QR code being the only way to access much of society...”

Lord Jonathan Sumption about freedom and democracy [retired justice UK supreme court]

[Liberal democracy will be the biggest casualty of this pandemic \(telegraph.co.uk\)](https://www.telegraph.co.uk/news/2021/01/14/liberal-democracy-will-be-the-biggest-casualty-of-this-pandemic/)

-“The biggest casualty of the lockdown will not be the closed pubs, restaurants and shops and the crippled airlines. It will not be our once-thriving musical, theatrical and sporting culture. It will not even be the wreckage of our economy. These are terrible things to behold. But the biggest casualty of all will be liberal democracy. Liberal democracy breaks down when frightened majorities demand mass coercion of their fellow citizens and call for our personal spaces to be invaded. These demands are invariably based on what people conceive to be the public good. They all assert that despotism is in the public interest.

...

A society in which oppressive control of every detail of our lives is unthinkable except when it is thought to be a good idea, is not free. It is not free while the controls are in place. And it is not free after they are lifted, because the new attitude will allow the same thing to happen again whenever there is enough public support. Liberty is not an absolute value, but it is a critically important, foundational one. Of all freedoms, the freedom to interact with other human beings is perhaps the most valuable. It is a basic human need, the essential condition of human happiness and creativity”

And a note about the Great Barrington Declaration:

Kulldorff M, Bhattacharya J. Kulldorff & Bhattacharya respond: The Collins and Fauci attack on traditional public health. Epoch Times. December 31, 2021.

-Discussed: the key scientific facts on which the GBD was based: a more than 1000-fold higher risk of death for the old compared to the young; the fundamental goal: get through this terrible pandemic with the least harm to the public’s health [health is broader than just COVID]. Also discuss that surprisingly, Fauci and Collins claimed focused protection of the old is impossible: but PH is fundamentally about focused protection; “lockdowns protected young low-risk affluent work-from-home professionals [such as administrators, scientists, professors, journalists, and lawyers], while older high-risk members of the working class were exposed and died in necessarily high numbers. This failure to understand that lockdowns could not protect the vulnerable”; and lockdown harms were an “extra heavy burden on the chronically ill, on children, for whom schools were closed, on the working class, especially those in densely populated inner cities, and on the global poor, with tens of millions suffering from malnutrition and starvation...”

4: Vaccine Mandates/Passports should not be used

a. The Efficacy of Vaccine Mandates is Unclear:

Golden A, Nimni G, Rao S, Rau N. Opinion: Why vaccine passports won't slow COVID spread, will hurt the poor and threaten medical ethics. Six good reasons to rethink vaccine certificates. National Post 2021; Sept 9.

-discusses that mandates have unclear benefits, overestimate vaccine effect on transmission, underestimate vaccine effect on protection from severe disease, ignore marginalized communities, and may contribute to inequality, loss of trust, and unintended consequences.

Subramanian SV, Kumar A. Increases in COVID-19 are unrelated to levels of vaccination across 68 countries and 2947 counties in the United States. Eur J Epidemiol 2021
<https://doi.org/10.1007/s10654-021-00808-7>.

-discusses the unclear efficacy of vaccine in controlling spread. For countries, there was “no discernable relationship between percentage of population fully vaccinated and new COVID-19 cases in the last 7 days. In fact, the trend line suggests a marginally positive association...” For US counties, “the median new COVID-19 cases per 100,000 people in the last 7 days is largely similar across the categories of percent population fully vaccinated... also appears to be no significant signaling of COVID-19 cases decreasing with higher percentages of population fully vaccinated.”

Mills MC, Ruttenauer T. The effect of mandatory COVID-19 certificates on vaccine uptake: synthetic-control modelling of six countries. Lancet Public Health 2021. [https://doi.org/10.1016/S2468-2667\(21\)00273-5](https://doi.org/10.1016/S2468-2667(21)00273-5).

-In Denmark and Germany, “did not find a clear effect of certification on vaccination rates”; the “effect on reported cases was difficult to assess on the basis of available data... for others (Israel and Denmark) we found a continued increase above the rate in control countries”; when there may have been an effect on vaccine uptake, most of the effect was in younger lower-risk age-groups [for France and Italy – “strong effect for those aged 18-24y and 25-49y, with smaller effects in older age groups”, and for France, Israel, Italy, and Switzerland data “suggests that those younger than 20y and aged 20-29y had increased uptake”].

Porat T, Burnell R, Calvo RA, Ford E, Paudyal P, Baxter WL, Parush A. “Vaccine Passports” may backfire: Findings from a cross-sectional study in the UK and Israel on willingness to get vaccinated against COVID-19. Vaccines 2021;9:902.

-Found that need frustration – particularly autonomy frustration – was associated with lower willingness to get vaccinated. Suggested that control measures, such as domestic vaccine passports, may have detrimental effects on people’s autonomy, motivation, and willingness to get vaccinated.

Prosser A, Helfer B, Streiner DL. Evaluating the number of unvaccinated people needed to exclude to prevent SARS-CoV-2 transmissions. medRxiv 2021. <https://doi.org/10.1101/2021.12.08.21267162>.

-using mid-to-end November/21 baseline infection risk [during Delta variant], the number needed to exclude was at least 1000 unvaccinated to prevent one transmission event in most types of settings. Concluded that the harms of exclusion [staffing shortages, unemployment, financial hardship, creation of a class of citizens who are not allowed to fully participate in many areas of society] may outweigh the benefits.

b. Why Efficacy is Unclear

i) Vaccine Efficacy (VE) waning over time, especially for infection and transmission

Puranik A, Lenehan PJ, Silvert E, Niesen MJM, Corchado-Garcia J, O'Horo JC, Virk A, et al. Comparison of two highly-effective mRNA vaccines for COVID-19 during periods of Alpha and Delta variants prevalence. medRxiv 2021. <https://doi.org/10.1101/2021.08.06.21261707>

-VE against infection: mRNA1273 86% (81, 90.6), BNT 76% (69, 81); in July 76% (58, 87), and 42% (13, 62). VE against hospitalization: mRNA1273 91.6% (81, 97), BNT 85% (73, 93); in July 81% (33, 96.3), and 75% (24, 93.9).

Tang P, Hasan MR, Chemaitelly H, Yassine HM, Benslimane FM, Al Khatib HA, AlMukdad S, et al. BNT162b and mRNA-1273 COVID-19 vaccine effectiveness against the Delta (B.1.617.2) variant in Qatar. medRxiv 2021. <https://doi.org/10.1101.2021.08.11.21261885>

-VE against any Delta infection: BNT 64.2% (38.1, 80.1) \geq 14d after first dose; 53.5% (43.9, 61.4) \geq 14d after second dose; for mRNA1273 79.0% (58.9, 90.1) and 84.8% (75.9, 90.8). VE against severe/critical/fatal Delta: \geq 14d after second dose BNT 89.7% (61.0, 98.1) and mRNA1273 100.0% (41.2, 100.0).

Chau NVV, Ngoc NM, Nguyet LA, Quang VM, Ny NTH, Khoa DB, et al. Transmission of SARS-CoV-2 Delta variant among vaccinated healthcare workers, Vietnam. medRxiv 2021

-investigation suggested ongoing transmission between the HCW, and that vaccine might not lower the infectivity of breakthrough cases

Wadman M. Israel's grim warning: Delta can overwhelm shots. With early vaccination and outstanding data, country is the world's real-life COVID-19 lab. Science 2021;373(6557):838-839.

-with 78% of those \geq 12y fully vaccinated, Israel is now logging one of the world's highest infection rates [nearly 700/M daily new cases; more than half in fully vaccinated people], suggesting that protection from infection wanes.

Subbaraman N. How do vaccinated people spread Delta? What the science says. Delta spreads more readily than other coronavirus variants among vaccinated people, data suggest. Nature 2021;596:327-328.

-emerging evidence suggests that Delta more likely than other variants to spread through vaccinated people; that vaccinated people who become infected with Delta can carry as much virus in their nose as do unvaccinated people; and that vaccines remain protective against serious illness and death

Mizrahi B, Lotan R, Kalkstein N, Peretz A, Perez G, Ben-Tov A, et al. Correlation of SARS-CoV-2 breakthrough infections to time-from-vaccine; Preliminary study. medRxiv 2021.

<https://doi.org/10.1101/2021.07.29.21261317>

-the risk for infection was significantly higher for early vaccinees compared to those vaccinated later

Scobie HM, Johnson AG, Suthar AB, Severson R, Alden NB, Balter S, et al. Monitoring incidence of COVID-19 cases, hospitalizations, and deaths, by vaccination status – 13 U.S. jurisdictions, April 4-July 17, 2021. MMWR. 2021;70.

-findings suggest a potential decline in vaccine protection against confirmed SARS-CoV-2 infection and continued strong protection against COVID-19-associated hospitalization and death

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Bajema KL, Dahl RM, Prill MM, Meites E, Rodriguez-Barradas MC, Marconi VC, et al. Effectiveness of COVID-19 mRNA vaccines against COVID-19-associated hospitalization – Five veterans affairs medical centers, United States, February 1-August 6, 2021. MMWR 2021;70.

-VE against hospitalization: similar before (Feb1-June30) and during (July1-Aug6) delta predominance: 84.1% vs 89.3%.

Grannis SJ, Rowley EA, Ong TC, Stenehjem E, Klein NP, DeSilva MB, et al. Interim estimates of COVID-19 vaccine effectiveness against COVID-19-associated emergency department or urgent care clinic encounters and hospitalizations among adults during SARS-CoV-2 B.1.617.2 (Delta) variant predominance – nine states, June-August 2021. MMWR 2021;70.

-VE estimates similar to before Delta became predominant: reaffirm high protection against moderate and severe COVID-19 resulting in emergency department, urgent care clinic, and hospital visits

Keehner J, Horton LE, Binkin NJ, Laurent LC, Pride D, Loghurst CA, et al. Resurgence of SARS-CoV-2 infection in a highly vaccinated health system workforce. NJEM 2021

-VE against symptomatic COVID-19 was >90% March to June/21, and 65.5% (48.9, 76.9) in July/21

News in Focus. COVID vaccine immunity is waning – how much does that matter? Nature 2021;597:606-607.

-steady decline in neutralizing antibody levels, growing risk of breakthrough infection over time, and in Israel elderly people who got vaccine at beginning of year seemed to have almost double risk of severe illness during July outbreak compared to more recent vaccinees

Acharya CB, Schrom J, Mitchell AM, Coil DA, Marquez C, Rojas S, et al. No significant difference in viral load between vaccinated and unvaccinated, asymptomatic and symptomatic groups infected with SARS-CoV-2 Delta variant. medRxiv 2021. <https://doi.org/10.1101/2021.09.28.21264262>.

-mean Ct-values (a surrogate for viral load) of vaccinated and unvaccinated no difference

Kissler SM, Fauver JR, Mack C, Tai CG, Breban MI, Watkins AE, et al. Viral dynamics of SARS-CoV-2 variants in vaccinated and unvaccinated persons. NEJM 2021.

-Examined infections in 37 vaccinated and 136 unvaccinated participants as part of the occupational health program of the NBA 28Nov/20 to 11Aug/21. There was no difference in mean peak viral load, but faster clearance time in vaccinated mean 5.5 (95% CrI 4.6, 6.5) vs. 7.5 (6.8, 8.2) days. However, for Ct values less than 25-30 (suggesting infectiousness), the difference on the graph appears to me at best less obvious.

Effect of Covid-19 vaccination on transmission of Alpha and Delta variants. NEJM. 2022. DOI: 10.1056.NEJMoa2116597.

-Aetrospective observational cohort study involving adult contacts [who were tested 1-10d after the index patient] of SARS-CoV-2-infected adult index patients from 1Jan-31July/21 from NHS contact tracing in England. Reduction in transmission were smaller for Delta than for Alpha variant. The reduction of transmission for Delta waned substantially: 2 doses BNT162b2 for each doubling of weeks the percentage of contacts with positive test increased by factor of 1.08 (1.95, 1.11), so at 2wk transmission reduced by 50% (35, 61), and at 12wk reduced by 24% (20, 28); 2 doses ChAdOx1 each doubling of weeks the percentage of contacts with positive test increased by factor of 1.13 (1.05, 1.21), so at 2wk transmission reduced by 24% (18, 30), and at 12wk reduced by 2% (-2, 6) [i.e., not reduced].

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Singanayagam A, Hakki S, Dunning J, Madon KJ, Crone MA, Koycheva A, et al. Community transmission and viral load kinetics of the SARS-CoV-2 delta (B.1.617.2) variant in vaccinated and unvaccinated individuals in the UK: a prospective, longitudinal, cohort study. Lancet Infect Dis 2021.
-Included 231 contacts exposed to 162 epidemiologically linked delta infected index cases in households and found the attack rate in household contacts was 25% (18, 33) in fully vaccinated contacts and 38% (24, 53) in unvaccinated contacts, with risk of infection increased with time in the 2-3 months since the second dose. This gave a VE 34% (-15, 60) [not statistically significant]. The attack rate in household contacts of fully vaccinated index cases was 25% (15, 35) similar to that from unvaccinated index cases 23% (15, 31).

Andrews N, Tessier E, Stowe J, Gower C, Kirsebom F, Simmons R, et al. Duration of protection against mild and severe disease by Covid-19 vaccines. NEJM 2022. DOI: 10.1056/NEJMoa2115481.

-A test-negative case-control design in England 8Dec/20 to 1Oct/21 in those with symptoms and tested up to 10d later; adjusted for age, sex, SES, race/ethnic group, geographic region, period, HCW, social care worker, clinical risk group (CRG: chronic conditions), clinically extremely vulnerable (CEV: highest risk), care home residence

VE for Delta	ChAdOx1		BNT162b2	
	2-9wk	20wk+ [25wk+ in age 65y+ symp]	2-9wk	20wk+ [25wk+ in age 65y+ symp]
Symptomatic COVID-19	67.6 (67.3, 67.9)	44.3 (43.2, 45.4)	89.7 (89.5, 89.8)	66.3 (65.7, 66.9)
Age 65y+	59.1 (55.4, 62.6)	27.8 (16.3, 37.8)	79.6 (77.0, 81.8)	51.8 (45.4, 57.4)
Hospitalization	95.2 (95.7, 95.7)	80.0 (76.8, 82.7)	98.7 (98.3, 99.0)	91.7 (90.2, 93.0)
65y+ CEV	78.6 (63.7, 87.4)	66.5 (47.9, 78.4)	95.7 (85.4, 98.7)	78.6 (66.6, 86.2)
40-64y CRG	93.7 (92.4, 94.8)	76.9 (65.2, 84.6)	98.2 (97.1, 98.8)	93.1 (84.3, 96.9)
Death	95.0 (93.1, 96.4)	84.8 (76.2, 90.3)	98.5 (96.5, 99.3)	91.9 (88.5, 94.3)

Ministry of Health Israel. Two-dose vaccination data. Government of Israel. 20.6.21 to 17.7.21. Side presentation updated to 18/7/21. https://www.gov.il/BlobFolder/reports/vaccine-efficacy-safety-follow-up-committee/he/files_publications_corona_two-dose-vaccination-data.pdf.

-VE for SARS-CoV-2 cases 39%, symptomatic COVID-19 40.5%, COVID-19 hospitalization 88.0%, severe COVID-19 91.4%. VE depended on time of vaccine completion Jan, Feb, Mar, April/21: for SARS-CoV-2 infection 16%, 44%, 67%, 75%; for symptomatic COVID-19 16%, 44%, 69%, 79%; for hospitalization and severe COVID-19 by April 83% and 84%

Chemaitelly H, Tang P, Hasan MR, AlMukdad S, Yassine HM, Benslimane FM, et al. Waning of BNT162b2 vaccine protection against SARS-CoV-2 infection in Qatar. NEJM 2021.

<https://doi.org/10.1056/NEJMoa2114114>.

-VE for any infection peaked by first month 77.5% (76.4, 78.6), declined gradually thereafter, accelerating after the 4th month: month 4 at 51.7% (45.0, 57.6), month 5 at 22.5% (10.6, 32.7), month 6 at 17.3% (2.2, 30.1), and month 7 at 22.3% (-1.7, 40.7). VE for symptomatic infection peaked month 1 at 81.5% (79.9, 83.0), and negligible by month 5 at 12.0% (-6.1, 27.1), and for asymptomatic peaked month 1 at 73.1% (70.3, 75.5), and negligible by month 4 at 11.5% (-17.1, 33.2). VE for any severe disease peaked in first 2 months at 96%+, and persisted at approximately this level for six months, with decline “possibly in the 7th month [55.6% (-44.3, 86.3)]... but the case numbers were small [only 6 and 11 cases]”. VE was similar for all ages and variants.

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Goldberg Y, Mandel M, Bar-On YM, Bodenheimer O, Freedman L, Haas EJ, et al. Waning immunity after the BNT162b2 vaccine in Israel. NEJM 2021.

-In those age 60+ the rate ratio for infection among those fully vaccinated in Jan/21 as compared with 2 months later in Mar/21 was 1.6 (1.3, 2.0), and in April/21 was 2.2 (1.6, 3.1). This meant the VE for those vaccinated May/21 was 82% and those vaccinated in Jan/21 was 57%. The rate ratio for severe disease between vaccination in Jan/21 and later in Mar/21 was 1.8 (1.1, 2.9). For those age 40-59 the rate ratio for infection among those fully vaccinated in Feb/21 as compared with 2 months later in April/21 was 1.7 (1.4, 2.1), and in May/21 was 2.1 (1.4, 3.0). This meant the VE for those vaccinated in May/21 was 83% and those vaccinated in Jan/21 was 57%. The rate ratio for severe disease between vaccination in Feb/21 and later in April/21 was 2.2 (0.6, 7.7). For those age 16-39y the rate ratio among those fully vaccinated in Mar/21 as compared with 2 months later in May/21 was 1.6 (1.3, 2.0), giving a VE for those vaccinated May of 80%, and for those vaccinated in Jan of 55%

Nordstrom P, Ballin M, Nordstrom A. Effectiveness of Covid-19 vaccination against symptomatic infection, hospitalization, and death up to 9 months: a Swedish total-population cohort study. Lancet Preprints 2021.

Vaccine	Peak	Waning	Ineffective	Risk groups
BNT162b2	D15-30 at 92% (92, 93)	D121-180 at 47% (39, 55)	D211+ 23% (-2, 41)	Age 80+; homemaker service, men
mRNA-1273	D15-30 at 96% (94, 97)	D181+ at 59% (18, 79)	-	As above
ChAdOx1	D15-30 at 68% (52, 79)	D61-120 at 41% (29, 51)	D121+ -19% (-97, 28)	As above
ChAdOx1/mRNA	D15-30 at 89% (79, 94)	D121+ 66% (41, 80)	-	As above
Severe	D15-30 at 95% (83, 93)	D121-180 at 74% (47, 87)	D181+ at 42% (-35, 75)	As above; any comorbidity

Shitrit P, Zuckerman NS, Mor O, Gottesman BS, Chowers M. Nosocomial outbreak caused by the SARS-CoV-2 Delta variant in a highly vaccinated population, Israel, July 2021. Euro Surveill 2021;26(39):pii=2100822.

-attack rates: staff 16/151 (10.6%), patients 23/97 (23.7%), despite exposed vaccination rate 96.2% at a median 177 (range 111 to 194) days earlier.

Tortof SY, Slezak JM, Fischer H, Hong V, Ackerson BK, Ranasinghe ON, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. Lancet 2021. [https://doi.org/10.1016/50140-6736\(21\)02183-8](https://doi.org/10.1016/50140-6736(21)02183-8).

VE against	First month	5 months after full vaccination
Infection	88% (86, 89)	47% (43, 51)
65y+	80% (73, 85)	43% (30, 54)
Other ages	Almost 90%	Similar degree of waning
Hospital admission	87% (82, 91)	88% (82, 92)

-most recent report Aug/21 from Israel suggests VE against hospital admissions has waned in 65y+ roughly at 6 months [vaccinated in Jan 54.8%; in March 81%; in April 69.4%]

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Lin DY, Gu Y, Wheeler B, Young H, Holloway S, Sunny SK, et al. Effectiveness of Covid-19 vaccines over a 9-month period in North Carolina. NEJM 2022. DOI: 10.1056/NEJMoa21172128.

-From 11Dec/20 to 8Sept/21 (Delta variant predominant), the VE against Covid-19 for BNT162b2 at 2 mos 94.5% (94.1, 94.) and at 7 mos 66.6% (65.2, 67.8); mRNA-1273 at 2 mos 95.9% (95.5, 96.2) and at 7 mos 80.3% (79.3, 81.2). VE against hospitalization and death was durable.

Cohn BA, Cirillo PM, Murphy CC, Krigbaum NY, Wallace AW. Breakthrough SARS-CoV-2 infections in 620,000 U.S. Veterans, February 1, 2021 to August 13, 2021. medRxiv 2021

<https://doi.org/10.1101/2021.10.13.21264966>

-In US Veterans age 18y+ receiving care in VHA in the period 1Feb/21 to 13Aug/21, vaccine protection declined over time at all ages. By August/21 the VE for infection was 3% (-7, 12) for Janssen, 64% (62, 66) for Moderna, and 50% (47, 52) for Pfizer-BioNTech.

Salvatore PP, Lee CC, Sleweon S, McCormick DW, Nicolae L, Knipe K, et al. Transmission potential of vaccinated and unvaccinated persons infected with the SARS-CoV-2 Delta variant in a federal prison, July-August 2021. medRxiv 2021 <https://doi.org/10.1101/2021.11.12.21265796>.

-In an outbreak of Delta in a federal prison Texas, there were no significant differences detected in duration RT-PCR positivity, Ct value on any day, or duration of viral-culture positivity between vaccinated and unvaccinated cases. The authors concluded that we “should consider vaccinated persons who become infected with SARS-CoV-2 to be no less infectious than unvaccinated persons.”

Hagan LM, McCormick DW, Lee C, Sleweon S, Nicolae L, Dixon T, et al. Outbreak of SARS-CoV-2 B.1.617.2 (Delta) variant infections among incarcerated persons in a federal prison – Texas, July-August 2021. MMWR 2021;70(38):1349-1354.

-In the Texas prison outbreak, infection occurred in 172/233 (74%) of incarcerated persons. The attack rate was higher in unvaccinated [39/42 (93%) vs. fully vaccinated 129/185 (70%) or partially vaccinated 4/6 (67%)] and in those vaccinated 4+ months prior [83/93 (89%) vs vaccinated 2wk-2mos prior 19/31 (61%) and vaccinated 2-4mos prior 27/61 (44%)]. By my calculation, this translates to a crude VE of 25%, and by 4+ months of 4%.

UK Health Security Agency. COVID-19 vaccine surveillance report. Week 42.

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1027511/Vaccine-surveillance-report-week-42.pdf

-Between week 38 and week 41 2021, as shown in Table 2 (page 13), case rates/100,000 were higher in unvaccinated than vaccinated at ages <18 and 18-29, but higher in vaccinated than unvaccinated at all other age groups [30-39, 40-49, 50-59, 60-69, 70-79, 80+]. This is shown graphically in Figure 2a (page 17).

Kampf G. The epidemiological relevance of the COVID-19-vaccinated population is increasing. Lancet Regional Health – Europe 2021;11:100272

-Discusses that it “appears to be grossly negligent to ignore the vaccinated population as a possible and relevant source of transmission.” Based on data including: a UK study finding the secondary attack rates among household contacts exposed to fully vaccinated index cases was similar to household contacts exposed to unvaccinated index cases (25% vs 23%); in Germany, the proportion of cases attributed to breakthrough infections in 60yo+ increased from 16.9% July/21 to 58.9% Oct/21; in UK, cases among 60yo+ between week 39 and 42 were among the fully vaccinated in 89.7% and unvaccinated in 3.4%; in Israel, a nosocomial outbreak involving 16 HCW and 23 patients (and 2 family members) from a fully vaccinated source despite fully vaccinated in 96.2% of exposed; and in US, the CDC identifies 4/5 counties with highest percentage of fully vaccinated population as ‘high’ transmission counties.

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Ioannidis JPA. Benefit of COVID-19 vaccination accounting for potential risk compensation. npj Vaccines. 2021;6:99.

-Discusses the effect of risk compensation [i.e., vaccine protection may increase people's risky behavior, such as meeting with more people, for lengthier periods, and/or in situations of higher infection risk, and with less adherence to distancing, masks, and/or testing]. If VE is 60% for infection, then even modest risk compensation will eliminate (if 'risky behavior' increases about 2.5-3X) or halve (if 'risky behavior' increases even <1.8-2X) the vaccine benefit.

Government of Canada. Statement from the Chief Public Health Officer of Canada on December 3, 2021. Public Health Agency of Canada.

-“emerging evidence on waning protection of vaccines over time... effectiveness against infection and symptomatic diseases decreases with time, and possibly against severe illness as well, especially in older individuals.”

Krause PR, Fleming TR, Peto R, Longini IM, Figueroa JP, Sterne JAC, et al. Considerations in boosting COVID-19 vaccine immune responses. Lancet 2021;398:1377-1380.

-Suggests that vaccines continue to be effective against severe disease, including by Delta variant, but less effective against asymptomatic disease or against transmission, with random effect meta-analysis finding VE for infection in those vaccinated less recently was 64.9% (56.6, 73.3). Also discusses that: vaccine supplies could save more lives if used in previously unvaccinated populations; could be risks from boosters if immune-mediated side-effects occur (such as myocarditis); observational data on efficacy of boosters could be confounded [e.g., some already protected because of previous infection; some deferred vaccination because of COVID-19 symptoms; high-risk individuals vaccinated earlier; different patterns of social interaction; collider bias due to different test seeking behavior] and may have only very short-term effect.

Krause PR, Gruber MF, Offit PA. We don't need universal booster shots. We need to reach the unvaccinated. Washington Post. November 29, 2021.

-Discusses that protection against serious illness is still strong, so the case for risking any side effects from vaccine diminishes substantially. The far more important task is of reaching vaccine holdouts [and it is wrong to assume that they are all unreachable]. Mentions “original antigenic sin” from boosters - repeatedly ‘training’ the immune system to fight the original virus could reduce the effectiveness of a variant-specific booster.

Grant JM. Vaccines will never eliminate COVID, so it's time to pivot our response. Toronto Sun. Nov 23, 2021.

-“SARS-CoV-2 is destined to become the 5th circulating coronavirus, with which everybody is eventually infected... vaccinated are still likely to be infected and transmit disease, with similar viral loads as those who are unvaccinated...” “It is not how many are vaccinated, but whom that matters”: people at risk of severe disease. “Effort needs to go to identifying communities of high-risk unvaccinated people, understanding their reasons for hesitancy and working with them towards acceptance of vaccines... Hospitalizations and deaths become the only metric that matters... We want high risk, non-immune, people to be vaccinated for their own protection and to reduce the impact on hospitals and healthcare systems...”

Rosenberg ES, Dorabawila V, Easton D, Bauer UE, Kumar J, Hoen R, et al. Covid-19 vaccine effectiveness in New York State. NEJM 2021. <https://doi.org/10.1056/NEJMoa2116063>

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-for adults 18y+ residing in NY state

Vaccine	VE in August/21 if vaccinated Jan/Feb/21		
	18-49y	50-64y	65y+
BNT162b2			
Covid-19	64.0% (60.5, 67.5)	71.1% (66.6, 75.6)	73.8% (73.3, 81.7)
Hospitalization	92.4% (87.8, 95.6)	94.4% (91.3, 96.6)	85.2% (82.4, 87.6)
mRNA-1273			
Covid-19	70.1% (67.1, 73.1)	74.7% (70.8, 78.6)	77.5% (73.3, 81.7)
Hospitalization	97.2% (94.3, 98.9)	96.8% (94.5, 98.3)	92.8% (90.4, 94.6)

Young-Xu Y, Zwain GM, Powell EI, Smith J. Estimated effectiveness of COVID-19 messenger RNA vaccination against SARS-CoV-2 infection among male veterans health administration enrollees, January to September 2021. JAMA Netw Open 2021;4(12):e2138975.

-In a case-control study using the Veterans Health Administration Corporate Data Warehouse, in the high-delta period the VE against laboratory confirmed infection was 62% (45.6, 73.5) in first month, 57.8% (52.5, 62.5) by month 3, and accelerated after month 4, reaching a low of approximately 20% in months 5 through 7.

Elliott P, Haw D, Wang H, Eales O, Walters CE, Ainslie KEC, et al. Exponential growth, high prevalence of SARS-CoV-2, and vaccine effectiveness associated with the Delta variant. Science 2021;374(1463):eabl9551.

-In the real time assessment of community transmission-1 (REACT-1) study in England, testing random samples of the population in round 12 (20May to 7June/21) and round 13 (24June to 12July/21), 44% of infections occurred in doubly vaccinated. VE against infection [adjusted for age, sex, region, ethnicity, index of multiple deprivation] was 49% (22, 67), and against symptomatic infection was 59% (23, 78).

ii) Natural Immunity is likely as good as or better than vaccine induced immunity

Vitale J, Mumoli N, Clerici P, De Paschale M, Evangelista I, Cei M, Mazzone A. Assessment of SARS-CoV-2 reinfection 1 year after primary infection in a population in Lombardy, Italy. JAMA Internal Medicine 2021 <https://doi.org/10.1001/jamainternmed.2021.2959>

-5 reinfections (0.31%, 95% CI 0.03, 0.58) in 1579 positive patients [1 was hospitalized] vs. 528 new infections (3.9%; 3.5, 4.2) in 13496 controls; adjusted IRR 0.07 (0.06, 0.08), HR 0.06 (0.05, 0.08). Suggests that natural immunity appears to confer a protective effect for at least a year

Rosenberg D. Natural infection vs vaccination: which gives more protection? Arutz Sheva Israel National News. July 13, 2021.

-from the Israeli Health Ministry: 835,792 known to have recovered from the virus, 72 cases, amounts to 0.0086% reinfections; 5,193,499 known to have been vaccinated, >3000 cases, amounts to 0.0578% breakthrough infections = >6.72X risk of infection in vaccinated vs. previously infected

Wadman M. Having SARS-CoV-2 once confers much greater immunity than a vaccine – but no infection parties, please. Science 2021 Aug 26.

-natural immune response after SARS-CoV-2 infection offers considerably more of a shield against the Delta variant than two doses of Pfizer-BioNTech vaccine. People who recover continue to develop increasing numbers and types of CoV-targeting antibodies for up to 1 year [in contrast, twice-vaccinated

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people stop seeing increases in the potency or breadth of the overall memory antibody compartment a few months after second dose].

Gazit S, Shlezinger R, Perez G, Lotan R, Peretz A, Ben-Tov A, Cohen D, Muhsen K, Chodick G, Patalon T. Comparing SARS-CoV-2 natural immunity to vaccine-induced immunity: reinfections versus breakthrough infections. medRxiv 2021 <https://doi.org/10.1101/2021.08.24.21262415>

-SARS-CoV-2 naïve vaccinees: 5.96 (4.85, 7.33) increased risk for breakthrough infection and 7.13 (5.51, 9.21) increased risk for symptomatic disease [and also a higher risk for hospitalization] compared to previously infected. Suggests that “natural immunity confers longer lasting and stronger protection against infection, symptomatic disease and hospitalization caused by the Delta variant”

Bertollini R, Chemaitelly H, Yassine HM, Al-Thani MH, Al-Khal A, Abu-Raddad LJ. Associations of vaccination and of prior infection with positive PCR test results for SARS-CoV-2 in airline passengers arriving in Qatar. JAMA 2021;326(2):185-188.

-Completely vaccinated: 10092 matched PCR + 0.82% (0.66, 1.01) vs 3.74% (3.37, 4.12); RR 0.22 (0.17, 0.28). Prior infection: 7694 matched PCR + 1.01% (0.80, 1.26) vs. 3.81% (3.39, 4.26); RR 0.26 (0.21, 0.34)

Radbruch A, Chang HD. A long-term perspective on immunity to COVID. Nature 2021;595:359-360.

-B and T cells specific for a virus maintained in dormancy, but poised to spring into action if encounter virus again. Findings predict that infection with SARS-CoV-2 induces long-term immunity in most individuals

Zuo J, Dowell AC, Pearce H, Verma K, Long HM, Begum J, et al. Robust SARS-CoV-2-specific T cell immunity is maintained at 6 months following primary infection. Nat Immunology 2021;22:620-626.

-reassuring that functional SARS-CoV-2-specific T cell responses are retained at 6 months following infection

Want Z, Muecksch F, Schaefer-Babajew, Flinkin S, Viant C, Gaebler C, et al. Naturally enhanced neutralizing breadth against SARS-CoV-2 one year after infection. Nature 2021;595:426

-findings suggest that immunity in convalescent individuals will be very long lasting

Kojima N, Shrestha NK, Klausner JD. A systematic review of the protective effect of prior SARS-CoV-2 infection on repeat infection. medRxiv 2021 <https://doi.org/10.1101/2021.08.27.21262741>

-10 studies eligible including 9.93M people with median observation ranging 1-10.3mos; weighted average risk reduction against reinfection 90.4% (SD 7.7%; range 80.5 to 100%), observed for up to 10 months

Block J. Vaccinating people who have had covid-19: why doesn't natural immunity count in the US? BMJ 2021;374:n2101

-memory B cells and memory T cells will respond by producing antibodies to the variants; over 20 references that natural immunity is durable up to 8 months after infection; studies in Qatar, England, Israel, and US suggest infection rates at equally low levels among fully vaccinated and previously infected; comparing symptomatic and asymptomatic the [highly functional] T-cell response was identical

Shrestha NK, Burke PC, Nowacki AS, Terpeluk P, Gordon SM. Necessity of COVID-19 vaccination in previously infected individuals. medRxiv 2021 <https://doi.org/10.1101/2021.06.01.21258176>.

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-cumulative incidence remained almost zero among healthcare workers previously infected unvaccinated (0/1359), previously infected vaccinated (0/1220), and previously uninfected vaccinated (15, 0.7% of infections), compared with steady increase among previously uninfected unvaccinated (2139, 99.3% of infections). Median duration since prior infection 143 [76, 179] days: suggesting protection for 10 months or longer

Cavanaugh AM, Spicer KB, Thoroughman D, Glick C, Winter K. Reduced risk of reinfection with SARS-CoV-2 after COVID-19 vaccination – Kentucky, May-June 2021. MMWR 2021;70(32):1081-1083.

-previous infection but not vaccinated OR 2.34 (1.58, 3.47) for reinfection compared to previous infection and fully vaccinated. Limitations include: the vaccinated may be less likely to seek testing because of believing in protection, the study was limited to 2 months (of 19 months of data) and 1 state (of all states with data), and was regardless of symptoms.

Bozio CH, Grannis SJ, Naleway AL, Ong TC, Butterfield KA, DeSilva MB, et al. Laboratory-confirmed COVID-19 among adults hospitalized with COVID-19-like illness with infection-induced or mRNA vaccine-induced SARS-CoV-2 immunity – Nine states, January-September 2021. MMWR 2021;70: Early Release

-In the VISION Network including 187 hospitals across 9 states, among COVID-like-illness hospitalizations in those whose previous infection or vaccination occurred 90-179d earlier, the aOR for confirmed COVID-19 among unvaccinated previously infected was 5.49 (2.75, 10.99) compared to those fully vaccinated with no previous infection. A crucial limitation is that only 7348/139,650 (5%) of eligible patients were included because only 67.5% were tested with hospitalization, and of these only 7.8% had a previous test done [required to determine if there was previous infection].

Qureshi A, Baskett WI, Huang W, Lobanova I, Naqvi H, Shyu CR. Re-infection with SARS-CoV-2 in patients undergoing serial laboratory testing. Clinical Infectious Diseases. 2021.

-Of 9119 prior infected patients with serial tests at 62 healthcare facilities in US from 1Dec/19 to 13Nov/20, reinfection occurred in 0.7%.

Canadian Covid Care Alliance. Which is better for future COVID-19 protection: Immunity following natural infection or vaccine-induced immunity? Reviewed by the CCCA Scientific and Medical Advisory Committee. October 8, 2021.

-Reviews more than 15 studies that suggest: natural immune responses, even to mild infections, were broader [including antibody, plasmablasts, memory B-cells, and T-cells, to many viral epitopes], durable, included mucosal immunity, and minimally impacted by variants. Re-infections were rare (<1%) with no study reporting an increase in reinfection over time. Although vaccination following natural infection may increase antibody titers to the Spike protein, this may not be required for further protection [vaccine responses are distinct from that of natural infection, and much less durable]. In fact, a second vaccine dose not only failed to boost antibodies, but determined a contraction of the S-specific T cell response.

Alexander PE. 141 research studies affirm naturally acquired immunity to COVID-19: documented, linked, and quoted. Brownstone Institute. October 17, 2021. <https://brownstone.org/articles/79-research-studies-affirm-naturally-acquired-immunity-to-covid-19-documented-linked-and-quoted/>

-Discusses studies that show naturally acquired immunity (to even mild infection) is equal to or more robust and superior to existing vaccines. Studies show infection effect on natural immunity, including antibodies, memory CD4+ and CD8+ T cells, memory B-cells, and long-lasting bone-marrow plasma cells,

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all of broader diversity than with vaccine. Studies also show clinical effect to prevent re-infection of 80-100% for at least 8 months.

Kojima N, Klausner JD. Protective immunity after recovery from SARS-CoV-2 infection. Lancet Infect Dis 2021. [https://doi.org/10.1016/S1473-3099\(21\)00676-9](https://doi.org/10.1016/S1473-3099(21)00676-9).

-A review that finds the risk of (repeat) SARS-CoV-2 infection is decreased by 80.5-100%, even after mild infections, persisting for more than 10 months of follow-up.

Murchu EO, Byrne P, Carty PG, De Gascun C, Keogan M, O'Neill M, et al. Quantifying the risk of SARS-CoV-2 reinfection over time. Rev Med Virol 2021;e2260.

-A review of 11 large cohort studies, finding that reinfection was an uncommon event (absolute rate median 0.27%; range 0-1.1%), with no study reporting an increase in the risk of reinfection over time.

Goldberg Y, Mandel M, Bar-On YM, Bodenheimer O, Freedman L, Ash N, et al. Protection and waning of natural and hybrid COVID-19 immunity. medRxiv 2021.

<https://doi.org/10.1101/2021.12.04.21267114>.

-data from the Israeli Ministry of Health database from Aug-Sept/21 in age 16y+, adjusting for age group, sex, population group, calendar week, and infections in past 7d in their area of residence.

Group	Infection rate per 100,000 risk-days	
	Previously infected or vaccinated 4-6mo ago	Previously infected or vaccinated 6-8 months ago
Unvaccinated previously infected	10.5 (8.8, 12.4)	14.0 (13.3, 14.8)
Single dose vaccinated following prior infection	10.3 (9.4, 11.4)	11.6 (10.0, 13.5)
Vaccinated and later infected	12.8 (9.9, 16.6)	17.2 (15.2, 19.2)
Vaccinated and previously uninfected	69.2 (68.8, 69.8)	88.9 (88.3, 89.6) [restored to 8.2 <2mos after booster]

Abu-Raddad LJ, Chemaitelly H, Bertollini R, for the National Study Group for COVID-19 Epidemiology. Severity of SARS-CoV-2 reinfections as compared with primary infections. NEJM 2021

-in Qatar from Feb/20 to April/21, reinfection patients were compared to matched patients with a primary infection [unvaccinated]. Severe disease at reinfection vs primary infection had OR 0.12 (0.03, 0.31), with no cases of critical disease or death at reinfection, and OR for composite outcome of severe, critical, or fatal disease at reinfection 0.10 (0.03, 0.25). Overall, the risk of having a severe reinfection is only approximately 1% of the risk of a previously uninfected person having a severe primary infection.

Kim P, Gordon SM, Sheehan MM, Rothberg MB. Duration of SARS-CoV-2 natural immunity and protection against the Delta variant: A retrospective cohort study. Clinical Infectious Diseases. 2021 DOI: [10.1093/cid/ciab999](https://doi.org/10.1093/cid/ciab999)

-At the Cleveland Clinic Health System in Ohio and Florida, among 325,157 patients tested before 31Dec/20, from 1July/21 to 0Sept/21, protection of prior infection against reinfection with Delta was 85.4% (80.0, 89.3). Among 152,656 patients tested before 30Aug/20, overall protection of previous infection was 85.7% (82.2, 88.5) and lasted up to 13 months.

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Chemaitelly H, Bertollini R, Abu-Raddad LJ, for the National Study group for COVID-19 Epidemiology. Efficacy of natural immunity against SARS-CoV-2 reinfection with the Beta variant. NEJM 2021. DOI: 10.1056/NEJMc2110300.

-In a retrospective matched-cohort study design in Qatar, natural infection protection against reinfection estimates were 92.3% (90.3, 93.8) for Beta, and 97.6% (95.7, 98.7) for Alpha, observed even 1 year after the primary infection.

Dowell AC, Butler MS, Jinks E, Tut G, Lancaster T, Sylla P, et al. Children develop robust and sustained cross-reactive spike-specific immune responses to SARS-CoV-2 infection. Nature Immunology 2021. DOI: 10.1038/s41590-021-01089-8.

-In children aged 3-11 years: neutralization of viral variants was comparable between children and adults; children retained antibody and cellular responses 6 months after infection, whereas relative waning occurred in adults; spike-specific responses were also broadly stable beyond 12 months.

Altarawneh H, Chemaitelly H, Tang P, Hasan MR, Qassim S, Ayoub HH, et al. Protection afforded by prior infection against SARS-CoV-2 reinfection with the Omicron variant. medRxiv 2022. <https://doi.org/10.1101/2022.01.05.22268782>.

-PE [effectiveness of prior infection in preventing reinfection] with Omicron, in a test-negative case-control study exact-matched by sex, age group, nationality, calendar time. The PE for symptomatic infection: 56.0% (50.6, 60.9); the PE for hospitalization or death: 87.8% (47.5, 97.1). None progressed to critical or fatal COVID-19.

Shrestha NK, Burke PC, Nowacki AS, Terpeluk P, Gordon SM. Necessity of COVID-19 vaccination in persons who have already had COVID-19. Clinical Infectious Diseases 2022. In Press.

-In employees of Cleveland Clinic working on 16Dec/20 followed until 27Dec/21; adjusted for age and patient facing job. Both prior COVID-19 and vaccination were independently associated with significantly lower risk of COVID-19. In previously infected individuals vaccination was not associated with significantly lower risk of COVID-19 pre-Omicron (HR 0.78; 0.31, 2.96) or in Omicron phase (HR 0.77; 0.53, 1.12), although it was associated with lower risk of symptomatic COVID-19 pre-Omicron (HR 0.60; 0.40, 0.90) and in Omicron phase (HR 0.36; 0.23, 0.57). In a subset of only those with prior infection, a significant risk with time since prior infection was not found for risk of COVID-19 or symptomatic COVID-19.

c. Concerns about vaccination in children: very low individual risk from COVID-19, and vaccine risk including myocarditis in young males.

Gur-Arie R, Kraaijeveld SR, Jamrozik E. An ethical analysis of vaccinating children against COVID-19: benefits, risks, and issues of global health equity. Wellcome Open Research 2021;6:252.

-Discusses several reasons not to mandate vaccinating children. First, the minimal benefit to healthy children, who are at similar or lower risk than that of typical seasonal influenza [and post-infection immunity likely more effective at protecting against re-infection later in life when disease would be more severe]. Second, potential for rare vaccine harms in children, which would undermine vaccine confidence in general [we now know of the myocarditis risk, for example]. Third, protecting risk groups does not require vaccinating children, because children account for a relatively small fraction of transmission, vaccines in these risk groups are highly effective against severe diseases, and vaccines cannot generate herd immunity. Fourth, perpetuation of global vaccine inequities, including that the social benefit [for adults and children] of vaccinating adults, particularly in LMICs, far outweighs the benefit of vaccinating healthy children in HICs.

Zimmermann P, Pittet LF, Finn A, Pollard AJ, Curtis N. Should children be vaccinated against COVID-19? Arch Dis Child 2021. <https://doi.org/10.1136/archdischild-2021-323040>.

-Discusses several considerations in vaccinating children. Arguments in favor are weak: a) protection against COVID [in children is generally mild, and no evidence of increasing severity; death risk is <0.005%; and many may already be immune and protected by vaccinated adults]; b) protection against MIS-C [which is rare (<0.1% of infected), resolves in vast majority, with mortality <1-2%; no evidence vaccine protects from it, or may not induce it]; c) protection against long-COVID [there may be no difference in prevalence of persistent symptom between infected and noninfected children]; and d) prevention of community transmission [but, transmission in educational settings is low and index cases are often adults; vaccine efficacy is waning, and infected vaccinated are as likely to transmit; once adults vaccinated (protected) this is less important; and once endemic, early childhood infection (which is mild) with subsequent boosting from ongoing exposure at older ages, may bring about population immunity more effectively]. Arguments against are stronger: a) risk of adverse events [myocarditis/pericarditis after mRNA vaccines (occurs in 1/6623 males 16-19y); of thrombosis after viral vector vaccines; and theoretical risk of inducing MIS-C]; b) long-term safety concerns [for which there is a lack of data, and which could undermine overall vaccine confidence]; and c) vaccine supply concerns [vaccines may be better prioritized for high-risk adults, including in LMIC].

Wong BLH, Ramsay ME, Ladhani SN. Should children be vaccinated against COVID-19 now? Arch Dis Child 2021;106(12):1147-1148.

-Discusses deaths in children being “extremely rare”, that children “do not contribute much to the spread”, that surveillance will be needed to “assess the risk of rare events [after vaccine], including immune-mediated conditions”, and that whether all children will eventually be vaccinated will depend on “the safety, effectiveness, and duration of protection afforded by available vaccines. Most importantly, it will depend on whether such vaccines interrupt transmission...”

Summary of the national advisory committee on immunization (NACI) statement of November 19, 2021. Recommendation on the use of the Pfizer-BioNTech COVID-19 vaccine (10 mcg) in children 5-11 years of age. Public Health Agency of Canada. 2021.

-A pediatric formulation (10 mcg compared to the adult 30 mcg) at a dosing interval of at least 8 weeks “may be offered”. The size of the trial “would not detect rare adverse events that may occur at a frequency less often than 1 in 1000 people.” Supports parents’ ability to “make an informed decision,” and that they “not stigmatized based on whichever choice they make.”

Sorg AL, Hugnagel M, Doenhardt M, Diffloth N, Schrotten H, v Kries R, et al. Risk of hospitalization, severe disease, and mortality due to COVID-19 and PIMS-TS in children with SARS-CoV-2 infection in Germany. medRxiv 2021. <https://doi.org/10.1101/2021.11.30.21267048>.

-In children <18yo, the risk of severe disease once infected was extremely low: hospitalization 0.359%, hospitalization that required any therapeutic interventions 0.065%, ICU admission 0.017%, CFR 0.0009% [and 5/13 of these had been in palliative care prior to infection; in those without comorbidity, CFR 0.0003%]. The lowest risk was in children 5-11yo without comorbidities, having ICU admission in 0.002% and no deaths. The rate of MIS-C was 1/4000 infections [none died, and approximately 50% required ICU admission], and the rate has likely been lower as the delta-variant has predominated.

Public Health Ontario. Myocarditis and Pericarditis following vaccination with COVID-19 mRNA vaccines in Ontario: December 13, 2020 to August 7, 2021. Toronto, ON: Queen’s Printer for Ontario; 2021.

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-204 reports met the case definition of myocarditis: mainly in adolescents/young adults - males aged 18-24y following second dose after Pfizer 37.4/M (1/26.7K) and after Moderna 263.2/M (1/3.8K) [7X higher]. Required an ED visit in 99%, hospitalization in 71.6%, and ICU in 1.5%.

Public Health Ontario. Adverse events following immunization (AEFIs) for COVID-19 in Ontario: December 13, 2020 to October 17, 2021. Toronto, ON: Queen's Printer for Ontario; 2021.

-age 12-17 and age 18-24 in males: dose 1 at 1/15K and 1/22.8K; dose 2 at 1/7962 and 1/5750; so overall in all males having vaccine the risk is the sum of dose 1 and 2 [because the doses do not overlap patients, as if one has myocarditis from dose 1 it is very unlikely you will get dose 2] = 1/5200 and 1/4591.

-In a similar update to data to Nov 7, 2021: dose 1 at 1/15K and 1/20K; dose 2 at 1/7490 and 1/5504; so, overall in males having vaccine the risk is the sum of dose 1 and 2 = 1/4996 and 1/4316

Witberg G, Barda N, Hoss S, Richter I, Wiessman M, Aviv Y, et al. Myocarditis after Covid-19 vaccination in a large health care organization. NEJM 2021. <https://doi.org/10.1056/NEJMoa2110737>.

-In Clalit Health Services, the largest HCO in Israel, myocarditis within 42d of first dose of vaccine [i.e., within only 21d of second dose] occurred in 54 people [41 mild, 12 intermediate, 1 fulminant]; 94% male; 69% after second dose (about 3-5d later). Hospitalization occurred for 49/54, for 3 [2, 4] days. There was 1 death the day after discharge from unspecified cause. In male patients 16-29y myocarditis after vaccine occurred in 10.69/100K (6.93, 14.46) = 1/12.2K.

Mevorach D, Anis E, Cedar N, Bromberg M, Haas EJ, Nadir E, et al. Myocarditis after BNT162b mRNA vaccine against Covid-19 in Israel. NEJM 2021. <https://doi.org/10.1056/NEJMoa2109730>.

-From 20Dec/20 to 31May/21 in Israel there were 136 definite or probable myocarditis cases after vaccine, 81% hospitalized, 91% male, 76% under 30y old, and clustered during the first few days after second dose. In males age 16-19y the risk difference between first (first 21d) and second (first 21d) doses was 13.73/100K (8.11, 19.46) = 1/7283; the standardized incidence ratio compared to historical rates, after the second dose was 13.60 (9.30, 19.20) [and 8.53 (5.57, 12.50) for males 20-24y; 6.96 (4.25, 10.75) for males 25-29y, and 2.90 (1.98, 4.09) for males 30y+]. Importantly, the rate ratio 30d after second dose compared to unvaccinated was 8.96 (4.50, 17.83), resulting in an excess 1/6637 (and only 1/99,953 for females) [for males 20-24y 6.13 (3.16, 11.88); for males 25-29y 3.58 (1.82, 7.01)]. Within 7 days of the second dose this was even higher for males 16-19y 31.90 (15.88, 64.08).

Truong DT, Dione A, Muniz JC, McHugh KE, Portman MA, Lambert LM, et al. Clinically suspected myocarditis temporally related to COVID-19 vaccination in adolescents and young adults. Circulation 2021.

-A retrospective multicenter study of patients <21yo presenting before 7/4/21 within 30d of vaccination with myocarditis. Of 139 cases, male in 90.6%, after second dose in 91.4% (a median 2 (IQR 1, 3) days after vaccine), with chest pain in 99.3% and ICU admission 18.7%. 80.6% had pseudo-infarct presentation with chest pain, ST changes on ECG, and elevated troponin with normal left ventricular systolic function [although 18.5% had at least mild heart dysfunction on echocardiogram]

Chua GT, Kwan MYW, Chui CSL, Smith RD, Cheung ECL, Mar TT, et al. Epidemiology of acute myocarditis/pericarditis in Hong Kong adolescents following Comirnaty vaccination. Clin Infectious Diseases. 2021.

-Describes an active pharmacovigilance system after COVID-19 vaccines in 12-17yo following Comirnaty vaccination from 14Jun/21 to 4Sept/21 in Hong Kong, to detect myocarditis/pericarditis within 14d of vaccine and admitted to hospital. Found 33 Chinese adolescents, 87.9% male, 81.8% after second dose,

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all with chest pain. Among male adolescents the incidence rate difference from background rate in 2020, after the first and second doses, were 5.36 (0.65,10.07) [1/18657] and 37.11 (25.10, 49.12) [1/2695] per 100,000 persons vaccinated [cumulative 1/2355].

Buchan SA, Seo CY, Johnson C, Alley S, Kwong JC, Nasreen S, et al. Epidemiology of myocarditis and pericarditis following mRNA vaccines in Ontario, Canada: by vaccine product, schedule and interval. medRxiv 2021. <https://doi.org/10.1101/2021.12.02.21267156>.

-Using passive vaccine surveillance data in Ontario from 14Dec/20 to 4Sept/21 there were 297 reports: 69.7% after second dose; 76.8% in males; 75% age <40y; 97.6% ED visit; 70.7% hospital admission (4.7% ICU); a median 3 [2, 8] days after vaccine. In males aged 18-24y the rates after second dose and cumulatively (after any dose) were for mRNA-1273 1/3339 and 1/2970, and for BNT162b2 1/16892 and 1/11710. In males aged 12-17 these rates for BNT162b2 were 1/10277 and 1/7605 (if the inter-dose interval was 30d or less, 1/6262 after second dose). In males aged 25-39 after mRNA-1273 these rates were 1/11099 and 1/8410. The highest rate after the second dose was in males 18-24y if first vaccine was BNT162b2 and second dose within 30d was mRNA-1273, at 1/2962.

Sharff KA, Dancoes DM, Longueil J, Johnson ES, Lewis PF. Risk of myopericarditis following COVID-19 mRNA vaccination in a large integrated health system: A comparison of completeness and timeliness of two methods. medRxiv 2021. <https://doi.org/10.1101/2021.12.21.21268209>.

-From Dec/20 to October/21 vaccination, in the Kaiser Permanente Northwest health system, using a method that searched all encounter diagnoses using a brief text description for “myocarditis” or “pericarditis”; reviewed to classify as confirmed or probable cases, identified approximately twice as many cases as CDC method. In those age 12-17y the risk was 1/5376, and in males after second dose 1/2650; for males age 18-24y after the second dose the risk was 1/1862.

Myocarditis from COVID-19 in young people is rare and of uncertain significance

Udelson JE, Rowin EJ, Maron BJ. Return to play for athletes after COVID-19 infection. The fog begins to clear. JAMA Cardiology 2021;6(9):997-999.

-review of several observational studies in athletes suggests those with detected COVID-19 have up to 0.9% incidence of cardiac magnetic resonance imaging (CMR) detected myocarditis. However, limitations include: the clinical implications of CMR detected abnormalities are unclear; interpretation of CMR was variable and non-standardized; there was no control group, and the denominators are unclear (i.e., how many infected that were not detected is unknown).

Martinez MW, Tucker AM, Bloom J, Green G, DiFiori JP, Solomon G, et al. Prevalence of inflammatory heart disease among professional athletes with prior COVID-19 infection who received systematic return-to-play cardiac screening. JAMA Cardiol 2021;6(7):745-752.

-Of 789 infected athletes, 5 (0.6%) ultimately had CMR suggesting inflammatory heart disease (3 myocarditis, 2 pericarditis), and no adverse cardiac events occurred.

Moulson N, Petek BJ, Drezner JA, Harmon KG, Kliethermes SA, Patel MR, et al. SARS-CoV-2 cardiac involvement in young competitive athletes. Circulation 2021;144:256-266.

-Of 3018 infected athletes, abnormal EKG occurred in 0.7%, troponin in 0.9%, ECHO in 0.9%, and CMR in 0.5%. Only 1 (0.03%) had an adverse cardiac event, likely unrelated to SARS-CoV-2 infection. Only 5 (0.2%) hospitalized, for non-cardiac reasons.

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Starekova J, Bluemke DA, Bradham WS, Eckhardt LL, Grist TM, Kusmirek JE, et al. Evaluation for myocarditis in competitive student athletes recovering from Coronavirus Disease 2019 with cardiac magnetic resonance imaging. JAMA Cardiol 2021;6(8):945-950.

-A review of health records of all competitive athletes recovering from COVID-19 who underwent CMR. Of 145 infected athletes, none were hospitalized, and 2 (1.4%) had CMR consistent with myocarditis, 1 of whom had 1 cm mild gadolinium enhancement and mild T2 signal abnormalities with normal laboratory values, and 1 had marked over multiple segments with elevated troponin.

Kotecha T, Knight DS, Razvi Y, Kumar K, Vimallesvaran K, Thornton G, et al. Patterns of myocardial injury in recovered troponin-positive COVID-19 patients assess by cardiovascular magnetic resonance. Eur Heart J 2021;42:1866-1878.

-148 patients 64 (12) years old with severe COVID-19 [all hospitalized; 32% ventilated in an ICU] and elevated troponin. Myocarditis-like scar detected in 32%, limited to 3 or less myocardial segments in 88% of cases, with no associated LV dysfunction, and no evidence of diffuse fibrosis or edema in the remote myocardium. “Myocarditis-like injury can be encountered, with limited extent and minimal functional consequence.”

Mandrola J, Foy A, Prasad V. Setting the record straight: There is no ‘Covid heart’. STAT May 14, 2021.

-discusses papers that find very low rate of symptomatic myocarditis requiring hospitalization in young athletes having COVID-19.

Joy G, Artico J, Kurdi H, Seraphim A, Lau C, Thornton GD, et al. Prospective case-control study of cardiovascular abnormalities 6 months following mild COVID-19 in healthcare workers. JACC 2021.

<https://doi.org/10.1016/j.jcmg.2021.04.011>

-found cardiovascular abnormalities, including by CMR, were no more common in infection positive vs infection negative healthcare workers 6 months later.

Myocarditis is very likely more common after vaccine than after SARS-CoV-2 in young males

Hoeg TB, Krug A, Stevenson J, Mandrola J. SARS-CoV-2 mRNA vaccination-associated myocarditis in children ages 12-17: A stratified national database analysis. medRxiv 2021

<https://doi.org/10.1101/2021.08.30.21262866>

-identified 257 cases of post-vaccine myocarditis in VAERS in USA: 15% after dose 1, 85% after dose 2; median 2d after (91.9% within 5d); hospitalization rate was 86.4% (86.2% age 12-15, 86.6% age 16-17)

Group	Myocarditis Rate/million		Compared to 120d COVID-19 hospitalization risk	
	One dose	Two doses	Without comorbidities	With comorbidity
Males 12-15y	12.0	162.2 (1/6.2K)	22.8X at low; 6.1X at moderate; 4.3X at high community rates	4.8X at low; 1.3X at moderate. COVID 1.09X at high community rates
Males 16-17y	8.2	94.0 (1/10.6K)	13.2X at low; 3.5X at moderate; 2.5X at high community rates	2.8X at low. COVID 1.34X at moderate, 1.88X at high community rates
Females 12-15y	0	13.0	-	-
Females 17-17y	2.0	13.4	-	-

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Boehmer TK, Kompaniyets L, Lavery AM, Hsu J, Ko JY, Yusuf H, et al. Association between COVID-19 and myocarditis using hospital-based administrative data – United States, March 2020-January 2021. MMWR 2021;70(35):1228-1232.

-Used the Premier Healthcare Database Special COVID-19 Release (PHD-SR) hospital-based administrative database of [inpatient or hospital-based outpatient] health encounters at >900 hospitals. The risk for myocarditis in those <16 years with COVID-19 was 0.133% (compared to those without COVID-19 this was an aRR 36.8 (25.0, 48.6) and aRD 0.122% (0.065, 0.179). For age 16-24y the aRR 7.4 (5.5, 9.2) and aRD 0.088% (0.061, 0.115). However, it is likely the risk for myocarditis with SARS-CoV-2 was at least 10X lower than this [given this study only included those diagnosed with COVID-19 at a hospital-based encounter], which would put the risk in those <16 years old at 0.0122%, or 1/8197, lower than from vaccination with an mRNA vaccine in males.

Dagan N, Barda N, Balicer RD. Adverse effects after BNT162b2 vaccine and SARS-CoV-2 infection, according to age and sex. NEJM 2021;385:2299.

Exposure	Condition in males 16-39 years old in Israel	
	Myocarditis per 100K	Pericarditis per 100K
Vaccination	8.62 (2.82, 14.35)	5.28 (0.17, 10.33)
Diagnosed infection	11.54 (2.48, 22.55)	11.30 (-1.38, 24.80)
Total SARS-CoV-2 infections*	Likely at least 5X lower	Likely at least 5X lower

*The total infections were not determined in the study. Given external data, it is very likely that the number of infections was at least 5X higher than the number of diagnosed cases of infection.

Patone M, Mei XW, Handunnetthi L, Dixon S, Zaccardi F, Shankar-Hari M, et al. Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. Nature Medicine 2021. <https://doi.org/10.1038/s41591-021-01630-0>

-In England, using data from hospital admissions and deaths from 1Dec/20 to 24Aug/21, the incidence rate ratios (IRR) for myocarditis were:

Group	BNT162b2		mRNA-1273		Infection IRR Excess cases
	IRR; Dose 1, 2 Excess cases	Cumulative	IRR; Dose 1, 2 Excess cases	Cumulative	
All ages	1.31 (1.03, 1.66); -		2.97 (1.34, 6.58); 9.94 (2.69, 36.03)		9.76 (7.51, 12.69)
Age under 40y	1.83 (1.20, 2.79); 3.40 (1.91, 6.04) 2 (1, 3)/M 3 (2, 4)/M	5/M (1/200K)	3.89 (1.60, 9.44); 20.71 (4.02, 106.68) 8 (4, 9)/M 15 (12, 16)/M	23/M (1/43K)	4.06 (2.21, 7.45) 10 (7, 11)/M (1/100K)
Men	-	-	3.79 (1.59, 9.04); 12.27 (2.77, 54.37)		9.06 (6.51, 12.62)
Men age under 40y	Not reported	-	Not reported	-	Not reported

-the study will undercount myocarditis after vaccine due to passive surveillance, and will overcount myocarditis after infection as high-sensitivity cardiac troponin is done on most SARS-CoV-2 cases and the denominator included only detected cases. Even so, the “risks [for myocarditis] are more evenly balanced [between vaccine and infection] in younger persons aged up to 40 years.”

Prasad V. Myocarditis under age 40: An update. Brownstone Institute. December 28, 2021.

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-Discusses the above study, pointing out that the denominator problem [for vaccines is known with precision, the true number of infections is unknown - if fixed using seroprevalence, would be even lower incidence after infection]; that the study lumps together men and women [a follow-up by that group found that men <40y after dose 2 and 3 of Pfizer, and after dose 1 and 2 of Moderna have more myocarditis than after SARS-CoV-2 infection]; and that the study does not separate age 16-24 [where myocarditis post-vaccine would likely look worst.

Patone M, Mei XW, Handunnetthi L, Dixon S, Zaccardi F, Shankar-Hari M, et al. Risk of myocarditis following sequential COVID-19 vaccinations by age and sex. medRxiv 2021.

<https://doi.org/10.1101/2021.12.23.21268276>.

-update to Nature Medicine paper referred to above by Prasad.

Group <40y	Dose 1 IRR	Dose 2 IRR	Dose 3 IRR	SARS-CoV-2 test+
Incidence Rate Ratio compared to baseline periods				
Males	BNT162b2 1.66 (1.14, 2.41); mRNA-1273 2.34 (1.03, 5.34)	ChAdOx1 2.57 (1.52, 4.35); BNT162b2 3.41 (2.44, 4.78); mRNA-1273 16.52 (9.10, 30.00)	BNT162b2 7.60 (2.44, 4.78)	2.02 (1.13, 3.61)
Females	-	mRNA-1273 7.55 (1.67, 34.12)	-	5.98 (2.83, 12.63)
Excess myocarditis events per million				
Males	3 (1, 5) 12 (1, 13)	14 (8, 17) 12 (1, 7) 101 (95, 104)	13 (7, 15)	7 (2, 11)
Females	-	8 (4, 9)	-	7 (6, 8)

-cumulative in males <40y: BNT162b2 2 doses 1/66.7K and 3 doses 1/35.7K; mRNA-1273 2 doses 1/8850. Compared to myocarditis after SARS-CoV-2 test positive of 1/142.9K

What drives emergence of Variants of Concern may be vaccine induced immunity

Kupferschmidt K. Startling new variant raises urgent questions Omicron’s many mutations look troubling but understanding its danger will take time. Science 2021;374(6572):1178-1180.

-mentions that “our antibodies and the spike protein are sort of in a genetic arms race”

Callaway E. Beyond Omicron: what’s next for SARS-CoV-2 evolution. The rapid spread of new variants offers clue to how the virus is adapting and how the pandemic will play out over the next several months. Nature 2021;600:204-207.

-mentions that the “forces propelling this ‘antigenic change’ are likely to grow stronger as most of the planet gains immunity to the virus through infection, vaccination or both... a global vaccination push that has delivered nearly 8 billion doses is shifting the evolutionary landscape... Omicron – rise may be largely due to its ability to infect people who are immune to Delta through vaccination or previous infection.”

Long-term safety is unknown, especially in children, from mRNA vaccines which are a completely new vaccine platform

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Stuart LM. In gratitude for mRNA vaccines. NEJM 2021;385:1436-1438.

-Discusses the history that led to the mRNA vaccines: modification of mRNA by replacing uridine with pseudo-uridine that attenuated immune activation, and being encapsulated and delivered by a lipid nanoparticle which boosted immunogenicity. However, in this article that asserted mRNA vaccines are known to be safe, the assertion of safety was based on one reference to a phase 1 dose-escalation study of mRNA influenza vaccine in 23 humans followed for 43 days.

Kostoff RN, Calina D, Kanduc D, Briggs MB, Vlachoyiannopoulos P, Svistunov AA, Tsatsakis A. Why are we vaccinating children against COVID-19? Toxicology Reports 2021;8:1665-1684.

-Discusses several points. First, COVID-19 attributed deaths per capita are negligible in children. Second, the normalized post-inoculation deaths reported to VAERS are small, but not negligible [from 14Dec/20 to 24May/21, after >285 million doses given in the US, there were 4863 reports of death in VAERS with strong clustering around the time of injection; and, historically, VAERS reported only 1% of actual vaccine/inoculation adverse events]. Unknown long-term effects could occur, and the vaccine trials did not address biomarkers that could serve as early warning indicators of predisposition to serious disease.

Gundry SR. mRNA COVID vaccines dramatically increase endothelial inflammatory markers and ACS risk as measured by the PULS cardiac test: A warning. Circulation 2021;144:A10712.

-566 patients seen in a preventive cardiology practice had new PULS test [“a clinically validated measurement of multiple protein biomarkers which generates a score predicting the 5-year risk of a new Acute Coronary Syndrome”] drawn 2-10 weeks after 2nd vaccine dose and compared to their previous score 3-5 months pre-vaccine. The PULS score increased from 11% to 25%. The conclusion was that “the mRNA vacs dramatically increase inflammation on the endothelium and T cell infiltration of cardiac muscle...”

d. Vaccine Mandates Worsen Inequality and Discriminate Marginalized Groups

Sacarny A, Daw JR. Inequities in COVID-19 vaccination rates in the 9 largest US cities. JAMA Health Forum 2021;2(9):e212415.

-found lower vaccination rates associated with being Black, Hispanic, or Latino; lower mean incomes and higher poverty rates, and lower college completion rates. Suggested this may be due to systematic underinvestment in public health in segregated communities; unequal access to health care information and services; and medical racism that drives legitimate mistrust among members of marginalized groups.

Dryden-Peterson S, Velasquez GE, Stopka TJ, Davey S, Gandhi R, Lockman S, Ojikutu BO. Disparities in SARS-CoV-2 vaccination-to-infection risk during the COVID-19 pandemic in Massachusetts. JAMA Health Forum 2021;2(9):e212666.

-found structural disparity in vaccine distribution: lower ratio of vaccine coverage to infection risk in communities with increased socioeconomic vulnerability and larger proportions of Black and Latinx individuals. Suggested that we had “prioritized large hospital systems and mass vaccination sites, rather than strategies to mitigate structural racism recommended by others”

Bibbins-Domingo K, Petersen M, Havlir D. Taking vaccine to where the virus is – Equity and effectiveness in Coronavirus vaccinations. JAMA Health Forum 2021;2(2):e210213.

-suggested incorporating place-based vaccine prioritization: bring vaccine to areas of high viral transmission according to zip-codes; use trusted messengers; take vaccination campaigns to the communities that have been hard-hit for too long

Corbie-Smith G. Vaccine hesitancy is a scapegoat for structural racism. JAMA Health Forum 2021;2(3):e210434.

-suggest that 'vaccine hesitancy' puts the focus on the individual. A better term is vaccine deliberation: "when I know that you care, I'll care about what you know"; when health care systems make shifts that demonstrate trustworthiness and a commitment to equity, more people will likely agree to take the vaccine. Should aim to provide support to both access appointments and travel to them; use mobile units and pop-up clinics preferably cosponsored by trusted local community; and have community leaders and organization fully engaged in planning and implementation.

Agarwal R, Dugas M, Ramaprasad J, Luo J, Li G, Gao G. Socioeconomic privilege and political ideology are associated with racial disparity in COVID-19 vaccination. PNAS 2021;118(33):e2107873118

-racism's "serious threat to public health": the weighted average COVID vaccine disparity across counties was 16% [white 35.9%, black 19.9%]. Not related to vaccine hesitancy; rather, related to social determinants of health [median income, high school education]. Needs a special effort to overcome barriers: access to resources and dissemination of accurate information.

Carson SL, Casillas A, Castellon-Lopez Y, Mansfield LN, Morris D, Barron J, et al. COVID-19 vaccine decision-making factors in racial and ethnic minority communities in Los Angeles, California. JAMA Netw Open 2021;4(9):e2127582.

-focus group results suggest a need to invest in community-based engagement, improve accessibility and transparency of information, and reduce structural barriers to vaccination.

Mello MM, Silverman RD, Omer SB. Ensuring uptake of vaccines against SARS-CoV-2. NEJM 2020;383(14):1296-1299.

-Support mechanisms for persons required to receive vaccine are necessary, especially for high-priority groups, with near-zero financial and logistic barriers [bringing to points of care, pharmacies, and work sites]. Also, need to build public trust with transparent, inclusive [representatives of high-risk population groups, and groups concerned about vaccine safety] planning.

Chagla Z, Ma H, Sander B, Baral SD, Moloney G, Mishra S. Assessment of the burden of SARS-CoV-2 variants of concern among essential workers in the greater Toronto area, Canada. JAMA Netw Open 2021;4(10):e2130284.

-cases and VOC were disproportionately associated with neighborhoods with lower income and with a higher proportion of essential workers. This "necessitates tailored and equitable intervention strategies including vaccine prioritization and outreach services."

McKinnon B, Quach C, Dube E, Nguyen CT, Zinszer K. Social inequalities in COVID-19 vaccine acceptance and uptake for children and adolescents in Montreal, Canada. Vaccine 2021;39:7140-7145.

-In 809 parents to 2-18yo responding to an online questionnaire 18May-26June/21, there were "marked social inequalities in COVID-19 vaccine acceptance and uptake." The authors concluded that interventions "should be tailored to meet local needs through active engagement and co-development with communities... efforts are needed to reach disadvantaged and marginalized populations with tailored strategies that promote informed decision making and facilitate access to vaccination."

e. Better messaging is important to reduce vaccine hesitancy and improve trust

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Ashworth M, Thunstrom L, Cherry TL, Newbold SC, Finnoff DC. Emphasize personal health benefits to boost COVID-19 vaccination rates. PNAS 2021;118(32):e2108225118.

-messaging that emphasizes personal health benefits has the largest impact; vaccine safety message did little to overcome a lack of confidence in vaccine

Patel MS. Text-message nudges encourage vaccination. Nature 2021;597:336-337.

-nudges using a single text message from a person's healthcare provider [to make the behavior easier, motivating people to take prompt action] increase vaccination rates.

Merkley E, Loewen PJ. Assessment of communication strategies for mitigating COVID-19 vaccine-specific hesitancy in Canada. JAMA Netw Open 2021;4(9):e2126635.

-an online survey suggested that communication strategies that focus on the death prevention potential (and not the comparatively less impressive overall effectiveness at preventing symptomatic transmission) are most effective.

Siegler AJ, Luisi N, Hall EW, Bradley H, Sanchez T, Lopman BA, Sullivan PS. Trajectory of COVID-19 vaccine hesitancy over time and association of initial vaccine hesitancy with subsequent vaccination. JAMA Netw Open 2021;4(9):e2126882.

-Vaccine hesitancy is not a stable trait precluding vaccination, but, instead, is labile: nearly one-third initially hesitant received vaccine, and more than one-third transitioned into vaccine willing. Vaccine willingness has not alleviated health inequities in vaccines received [baseline vaccine willingness similar for White and Hispanic, yet at follow-up fewer Hispanic were vaccinated].

Assistant Secretary for Planning Evaluation ASPE. Issue Brief August 2021. Unvaccinated for COVID-19 but willing: Demographic factors, geographic patterns, and changes over time.

-approximately 30% of US adults are unvaccinated, and among these, approximately 44% may be willing [the proportion of willing is higher among young adults, Blacks, Hispanics, and uninsured].

Doidge N. Needle Points: Why so many are hesitant to get the COVID vaccine, and what we can do about it. Table Magazine. October 27, 2021 (38 Pages).

-Discusses the many good historical and contemporary reasons people may have an "absence of faith in the wider systems that brought us the vaccines", and that public health "must be rooted not in coercion but in confidence, and not only among the majority". Mentions there is emerging "a new kind of scientific ideology, which we might call "vaccinism", which is insulted by the idea of any exemptions... it is the ideological mirror of anti-vaxxism."

f. Vaccine equity internationally is being ignored

Cohen J. Vaccine equity hopes dashed. Latest forecast slashes this year's global supply by 25%. Science 2021;373(6561):1297.

-only 1.9% of people in low-income countries have received a single dose; in India only 12% were fully vaccinated. Quotes the WHO director general Tedros Ghebreyesus saying: "the companies and countries that control the global supply of vaccines think the world's poor should be satisfied with leftovers."

Msomi N, Lessells R, Mlisana K, de Oliveira T. Africa: tackle HIV and COVID-19 together. Failure to get COVID-19 vaccines to nations with high rates of uncontrolled advanced HIV puts people living with that virus at even greater risk, and could drive the emergence of coronavirus variants. Nature 2021;600:33-36.

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-Discusses that people with uncontrolled advanced HIV could lead to the emergence of variants because they can be infected with SARS-CoV-2 for several weeks or months. In Sub-Saharan Africa, home to 2/3 of people living with HIV (8M, or around 1/3, of whom are not receiving effective antiretroviral therapy), as of mid-Nov/21 only <7% of people are fully vaccinated.

Pai M, Olatunbosun-Alakija A. Vax the world. Science 2021;374(6571):1031.

-only 2.5% of the population of LIC are fully protected [3.5 billion people are waiting for their first dose], and yet COVID-19 has rolled back most of the global gains in tackling poverty [100 million more people] and disease [disrupted essential health services including routine immunization, health services for TB, malaria, and HIV, and treatment of many common non-communicable diseases]

Kupferschmidt K. Missed shots. By total doses delivered, the COVID-19 vaccine rollout was a spectacular success. By other measures, it went tragically awry. Science 2021;374(6574):1434-1435.

-discusses several problems with the vaccines, including that protection began to wane [“any hopes that the vaccines might curb transmission enough to stop the virus from spreading have proved ill-founded”; “herd immunity, always an ambitious goal, slipped out of reach”]; and that “rich countries... cornered the market for vaccines” [only 8% of Africa’s population is fully vaccinated].

5. Emergency Management as a better *process* for a public emergency

Joffe AR, Redman D. The SARS-CoV-2 pandemic in high income countries such as Canada: A better way forward without lockdowns. 2021 OSF Preprints. <https://doi.org/10.31219/osf.io/r8d6f>. Now in press at: <https://www.frontiersin.org/articles/10.3389/fpubh.2021.715904/abstract>

-discusses the Emergency Management process, and resulting priorities to address in managing the society-wide emergency of the pandemic

Redman D. Position Paper. Canada's deadly response to COVID-19. Frontier Center for Public Policy. Policy Series No. 237. July 2021. https://fcpp.org/wp-content/uploads/FC-PS237_CDADeadlyResponse_JL1621_F2.pdf

-discusses how government and medical officers of health did not follow the Emergency Management process, and what a response informed by EM principles and process should look like

Jung AS, Haldane V, Neill R, Wu S, Jamieson M, Verma M, et al. COVID-19 preparedness and response: implications for future pandemics. National responses to covid-19: drivers, complexities, and uncertainties in the first year of the pandemic. *BMJ* 2021;375:e068954.

-Presents a framework for pandemic management that is remarkably similar [though less comprehensive] than the Emergency Management process. Discusses three pillars: governance [including leadership and coordination, with scientific advice taken into consideration; financing; community engagement; accountability; wide representation], control strategies [aggressive containment, suppression, vs mitigation strategy, with a clear goal], and interventions [with monitoring and evaluation]. Discusses that management should consider the broader multidimensionality of health, including the inner and outer contexts, drivers [underlying and systemic inequalities, vulnerabilities, and fragilities on which health and wellbeing are built on], and complexities [health and wellbeing are equally intertwined with social, economic, political, and ecological circumstances; the importance of upholding human rights and protecting lives and livelihoods].

Some comments about healthcare surge capacity

Furey A. It's time hospital CEOs faced some public scrutiny. *Toronto Sun*. Nov 6, 2021.

<https://torontosun.com/opinion/columnists/furey-its-time-hospital-ceos-faced-some-public-scrutiny>

-“we've known for a long time that capacity was a challenge [but the months ticked by]: so each time the argument is used, the public should be less willing to accept it because the powers that be have had that much more time to solve the underlying problems... some of the highest paid public servants in the country are healthcare administrators... only to turn around and tell that same public that hospital capacity issues are in fact their responsibility, because they didn't 'stay home' enough, and that the solution lies not in how those CEOs are managing their own tasks, but that it is in fact the public that must 'do more'...”

Furey A. This is now all about hospital capacity – so why isn't it better after 2 years? *Toronto Sun*. Dec 16, 2021.

-“The question we now need to ask is how is it that after almost two years of concern around hospital capacity we find ourselves almost back to square one, where a relatively small number of seriously ill people is enough to cause so much calamity for such a large and well-funded system... That's a rather odd idea, isn't it? That it's up to us to protect the hospitals... you'll notice that there's already a whole lot of people each paid a whole lot of money to protect the hospitals... They're the ones who need to do more.”

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Newport A. Lockdowns are no longer acceptable 2 years into the pandemic in Ontario. Insauga.com. Jan 7, 2022.

-Despite two years of preparation time, huge vaccine uptake and a very compliant population, we're pretty much back to where we were this time last year... [because of] our shockingly fragile health care system... Too many people feel it is their virtuous duty to continue to sacrifice for the sake of the healthcare system... scare[d]... into believing that they must continue to sacrifice their livelihoods and mental health to serve a healthcare system that is supposed to serve and protect them. A healthcare system that they pay into quite handsomely... At this point, it's time to force smarter investment in healthcare and different solutions to expected outbreaks by refusing to accept that 'hunkering down' is the only way to respond to the transmission of a highly contagious virus. We cannot keep doing this every time the temperature drops in Ontario."

Ruess H. Canadian health care desperately needs an HBO moment. Why is Canadian health care the greatest in the world? It isn't. The Line [Substack]. Jan 12, 2022.

-According to OECD data, Canadian rank is – for life expectancy 16th, mortality rates from avoidable causes 23rd, cancer survival rates 13-18th, 1-year-olds vaccinated for dTP 37th, spending as proportion of GDP 7th. "Canada spends a disproportionately large amount of money to get strongly mediocre health outcomes." "Our hospitals operate at or near capacity at the very best of times. We are ill-equipped to handle minor health crisis like annual flu seasons... Protecting our dangerously fragile system is why we're some of the most locked down people on the entire planet right now... our health-care system must do better..."

Furey A. Here's what's really going on in Ontario hospitals. Toronto Sun. Jan 10, 2022.

-Discusses that "A lot of the problems, say people on the frontlines, are being worsened and even created by antiquated policies and poor management on the part of administrators". This includes transfer problems [nowhere to send patients who have recovered], and staffing issues - too many staff have been placed in isolation and aren't allowed to work, many who have decreased their workload due to need to supervise kids during online learning, those deemed a close contact are to be sent home, staff who test positive for the virus and are asymptomatic cannot work, firing of unvaccinated nurses, and incredible disrespect shown to nurses by management [e.g., doctors given danger pay but nurses not].

McCullough JJ. Canada's media has found a new explanation for its covid crisis. Washington Post. Jan 13, 2022.

-"Canadian hospitals continued to be packed to the rafters with cases – prompting canceled surgeries, closed classrooms, perpetually extended lockdowns, and frantic gimmicks such as Quebec's 'anti-vax-tax'... Maybe, all along, it was about the deficiencies of Canada's much-vaunted public health-care system."

Some comments about enough is enough

Furey A. Ontarians are locked down again – and that's unacceptable. Toronto Sun. Jan 3, 2022.

-"Its time to say enough is enough... it is simply not acceptable that children should be denied schooling and society shut down because a G7 nation's hospital system is somehow threatened by such volume... after almost two years of prep time, it's a scandal that people who are supposedly well-suited to their jobs are still trotting out these old arguments... someone whose actual job is to protect the hospitals tries to flip it around on them [parents] and tell them that it's in fact the job of their children to protect

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hospitals... Maybe it's time to get some of them off the field, end this unjustified lockdown and get in people who can rise to the occasion."

Sun Media. Editorial: What's the end point to all of this? Toronto Sun. Jan 3, 2022.

-“The answer, according to officials, is due to concerns around hospital capacity. Guess what? That's not the problem of regular folks. They pay a whole lot of tax dollars for what should be a world-class healthcare system... COVID-19 is not going away anytime soon. It's anticipated to always surge during traditional virus season... Enough is enough. This can't go on and people are within their rights to say so.”

Bercovici V. Israeli public wising up to COVID hysterics. National Post. Dec 23, 2021.

-“A rational society operates on the basis of probability, which is determined by an informed assessment of sound evidence. Liberal democracies have become a club of self-affirming hysterics. What the leaders of these countries ought to understand is that their dystopian moment is over. The masses have wised up. Time to get real.”

Proudfoot S. The cruel, ridiculous reality of 'virtual learning'. What does online school actually look like? It's an impossible balancing act that's ruining kids and parents alike. And it's not okay. Macleans Magazine. January 5, 2022.

-“But the longer we keep finding a way to soldier through this, the more it feels like we are aiding and abetting the colossal lie that this is okay, that this was a reasonable and necessary choice, that there is not massive damage being sustained by these decisions every day, with the full, horrifying toll unknowable for years... No one is fine here. This is not okay... But this is not a real education or a real childhood. We should all stop playing along like it is.”

Studin I. Premier Ford has betrayed Ontario's youth. Toronto Sun. Jan 4, 2022.

-“This posture of conspicuous, expressive policy and administrative cruelty toward our youth – the future – must end now... The schools must open forthwith, and never close again. And all youth sports, music and extracurriculars must resume without condition, fetish or hysteria. Full normalization for our kids now.”

Chartier N. CBC producer resigns, cites public broadcaster's 'radical political agenda'. Epoch Times. Jan 4, 2022.

-veteran journalist Tara Henley wrote about CBC on Substack: “churning out clickbait that reads like a parody of the student press... It is to allow sweeping societal changes like lockdowns, vaccine mandates, and school closures to roll out – with little debate. To see billionaires amass extraordinary wealth and bureaucrats amass enormous power – with little scrutiny. And to watch the most vulnerable among us die of drug overdoses – with little comment...”

Makary M. America's elite universities are defying science and reason by clinging to cruel COVID policies that we now know cause more harm than good. DailyMail.com. Jan 4, 2022.

-“Universities are supposed to be bastions of critical thinking, reason and logic. But the Covid policies they have adopted – policies that have derailed two years of students' education and threaten to upend the upcoming spring semester – have exposed them as nonsensical, anti-scientific and often downright cruel... the data simply do not justify any of it... It's time for them to speak out... The medical establishment is intoxicated with groupthink... Concerned citizens should challenge medical dogma with data. It's time to learn to live with Covid by using some common sense practices.”

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Gandhi M, Noble J. We can't just impose restrictions whenever COVID-19 surges. Here's a better plan for 2022. Time Magazine. Dec 22, 2021.

-"[With Omicron] a more appropriate goal of protecting those at risk of severe breakthrough infections is now in order... restrictions [are] based on metrics that are no longer clinically relevant [the relationship between case counts and hospitalizations has been uncoupled]... it is time to reframe our approach, moving beyond case counts and community-based restrictions and revising policies specifically aimed at protecting vulnerable populations and assuring that our nation's children will stay in school."

Peterson J. Open the damn country back up, before Canadians wreck something we can't fix. The country is growing more authoritarian in response to fear. National Post. Jan 10, 2022.

-"We are pushing the complex systems upon which we depend and which are miraculously effective and efficient in their often thankless operation to their breaking point... These systems are now shaking. We're compromising them seriously with the unending and unpredictable stream of restrictions, lockdowns, regulations and curfews... The cure has become worse than the disease... There is no end game... How long are going to flail about, hiding behind our masks, afraid to send our children (who are in no danger more serious than risk of the flu) to school, charging university students full tuition for tenth-rate online 'education'... compromising the great economic engine upon which our health also depends? Until we decide not to. There are no risk-free paths forward. There is only one risk, or another. Pick your poison: that's the choice life often offers. I am weary of living under the increasingly authoritarian dictates of a polity hyper-concerned with one risk, and oblivious to all others... Enough, Canadians... Set a date. Open the damn country back up, before we wreck something we can't fix. Time for some courage. Let's live again."

6. How Pandemics End:

Robertson D, Doshi P. The end of the pandemic will not be televised. BMJ 2021;375:e068094.
<http://dx.doi.org/10.1136/bmj-2021-068094>.

-pandemic “endings are not clear cut, and that pandemic closure is better understood as occurring with the resumption of social life, not the achievement of specific epidemiological targets. Respiratory pandemics of the past 130 years have been followed by annual seasonal waves fueled by viral endemicity that typically continues until the next pandemic... The notion, reinforced by dashboards, that a pandemic ends when cases or deaths drop to zero is at odds with the historical evidence that substantial influenza morbidity and mortality continues to occur, season after season, between pandemics... [the end of the pandemic] will occur gradually and unevenly as societies cease to be all consumed by the pandemic’s shocking metrics. Pandemic ending is more a question of lived experience, and thus is more of a sociological phenomenon than a biological one... Far from a dramatic “end,” pandemics gradually fade as society adjusts to living with the new disease agent and social life returns to normal... **Covid-19 pandemic will be over when we turn off our screens and decide that other issues are once again worthy of our attention.**”

Anonymous. COVID is here to stay: countries must decide how to adapt. Nature 2022;601:165.

-“2022 is the year the world must come to terms with the fact that SARS-CoV-2 is here to stay... what is clear is that the hope that vaccines and prior infection could generate herd immunity to COVID-19 – an unlikely possibility from the start – has all but disappeared. It is widely thought that SARS-CoV-2 will become endemic rather than extinct... we must be ready to adapt with it.”

Emanuel EJ, Osterholm M, Groner CR. A national strategy for the “New Normal” of life with COVID. JAMA 2022. DOI: 10.1001/jama.2021.24282.

-“As the Omicron variant of SARS-CoV-2 demonstrates, **COVID-19 is here to stay**... Policy makers need to specify the goals and strategies for the ‘new normal’ of life with COVID-19 and communicate them clearly to the public... The goal for the ‘new normal’ with COVID-19 does not include eradication or elimination, eg, the ‘zero COVID’ strategy... The ‘new normal’ requires recognizing that SARS-CoV-2 is but one of several circulating respiratory viruses.”

Black C. In the face of Omicron, Canada once again cowers in unnecessary fear. National Post. Jan 15, 2022.

-“It is time for practically every jurisdiction in the western world to acknowledge that they have dismally failed to manage the COVID crisis... It was over-hyped and accorded an almost terrorizing quality... largely suppressing the facts that 80% of fatalities had other significant medical problems, that 80% of fatalities occurred among people over the age of 65 and that the disease did not present a huge risk for young, healthy people. Over 99% of people under 65 survive it... little media interest in exploring the consequences of such a lockdown [for the school population, private sector, government debt]... the cowardice of the federal and most of the provincial oppositions... Shuttering everything down again because of Omicron [which is much less severe] is insane, and postpones a fast ticket to general public immunity and the end of the crisis... there is no sign that the various governments of Canada have figured out much of this.”

Murray CJL. COVID-19 will continue but the end of the pandemic is near. Lancet 2022.
[https://doi.org/10.1016/S0140-6736\(22\)00100-3](https://doi.org/10.1016/S0140-6736(22)00100-3).

-“COVID-19 will become another recurrent disease that health systems and societies will have to manage. For example, the death toll from Omicron seems to be similar in most countries to the level of

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a bad influenza season.... The era of extraordinary measures by government and societies to control SARS-CoV-2 transmission will be over. After the Omicron wave, COVID-19 will return but the pandemic will not.”

Omicron is a milder variant of SARS-CoV-2

Callaway E, Ledford H. How bad is Omicron? What scientists know so far. COVID researchers are working at breakneck speed to learn about the variant’s transmissibility, severity and ability to evade vaccines. Nature 2021;600:197-199.

-discusses that travel bans could discourage governments from sharing genomic surveillance data [by punishing those who did a good job]; and that there’s going to be “unhinging” of the case rate in the community compared to the hospitalization rate [because Omicron is milder].

Callaway E. Beyond Omicron: what’s next for SARS-CoV-2 evolution. The rapid spread of new variants offers clue to how the virus is adapting and how the pandemic will play out over the next several months. Nature 2021;600:204-207.

-Discusses that SARS-CoV-2 has become endemic, becoming the 5th HCoV to permanently establish itself in humans; and that endemic SARS-CoV-2 will be likely to cause outbreaks and epidemics of varying size each year, likely becoming largely an infection in children, and with mostly mild symptoms in adults.

Espenhain L, Funk T, Overvad M, Edslev SM, Fonager J, Ignham AC, et al. Epidemiological characterization of the first 785 SARS-CoV-2 Omicron variant cases in Denmark, December 2021. EuroSurveillance. 2021.

-by 9Dec/21, there were 785 Omicron cases in Denmark, most in fully (76%) or booster-vaccinated (7.1%), with 9 (1.2%) hospitalized, 1 (0.13%) in ICU, 0 deaths.

Wang L, Berger NA, Kaelber DC, Davis PB, Volkow ND, Xu R. Comparison of outcomes from COVID infection in pediatric and adult patients before and after the emergence of Omicron. medRxiv 2021. <https://doi.org/10.1101/2021.12.20.21268495>

-In a retrospective cohort study using a US database (TriNetX Analytics Network Platform), VE was compared between Emergent Omicron Cohort 12/15-12/24/21 (n=14,054); Delta Cohort 9/1-11/15/21 (n=563,884), Delta-2 Cohort 11/16-11/30/21 (n=77,692), matched (n=14,040) for demographics, SES, comorbidities, medication, vaccine. The prevalence of Omicron during 12/15-12/24 was only 22.5-58.6%, suggesting that the outcomes for Omicron may be found to be even milder than what was reported here as the prevalence of Omicron increases.

3-day Risk	All	0-4y	5-11y	12-17y	18-64y	≥65y
ED Visit	RR 0.30 (0.28, 0.33)	0.19 (0.14, 0.25)	0.29 (0.21, 0.39)	0.16 (0.11, 0.24)	0.32 (0.27, 0.34)	0.53 (0.44, 0.63)
Hospitalization	RR 0.44 (0.38, 0.52)	0.36 (0.19, 0.68)	0.53 (0.25, 1.13)	0.63 (0.33, 1.19)	0.32 (0.25, 0.40)	0.55 (0.44, 0.68)
ICU admission	RR 0.33 (0.23, 0.48)					
Mechanical Ventilation	RR 0.16 (0.08, 0.32)					

Policy Lab. Omicron data supports resuming in-person education in the new year: A statement from the PolicyLab at Children’s Hospital of Philadelphia. Dec 31, 2021.

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-this new variant has been milder than earlier COVID-19 strains for most children, and is occurring during a time when all K-12 students and their caregivers have been offered vaccination

Maslo C, Friedland R, Toubkin M, Laubscher A, Akaloo T, Kama B. Characteristics and outcomes of hospitalized patients in South Africa during the COVID-19 Omicron wave compared with previous waves. JAMA 2021. DOI: 10.1001/jama.2021.24868.

-A Netcare private health care group of 49 acute care hospitals across South Africa, through 20Dec/21. Patients presenting to the ED with positive COVID-19 test result and admitted, 68-69% in first 3 waves, 41.3% in wave 4; patients requiring oxygen therapy, 74% wave 3 and 17.6% wave 4; ICU admission, 29.9% wave 3, 18.5% wave 4; median LOS, 7-8d in first 3 waves, 3d in wave 4; death rate, 19.7% wave 1, 29.1% wave 3, 2.7% in wave 4.

Abdullah F, Myers J, Basu D, Tintinger G, Ueckermann V, Mathebula M, et al. Decreased severity of disease during the first global Omicron variant COVID-19 outbreak in a large hospital in Tshwane, South Africa. Int J Infect Dis 2021. <https://doi.org/10.1016/j.ijid.2021.12.36357>.

-466 hospital COVID-19 admissions since 14Nov/21, and reviewed 98 patient records at peak bed occupancy. Deaths: 4.5% vs 21.3% (<0.00001); ICU admissions 1% vs 4.3% (p=0.0007); LOS 4.0 vs 8.8d (p<0.00001); 6 PICU admission unrelated to COVID and no pediatric deaths. Peak bed occupancy at 51% previous highest peak; 63% had incidental COVID-19 [only 1/3 had COVID pneumonia, of which 72% had mild to moderate disease]. Data showed decoupling of cases, hospitalizations, and deaths compared to previous waves in Tshwane and the Guateng Province as a whole. The authors conclude their data is "suggesting that Omicron may be a harbinger of the end of the epidemic phase of the Covid pandemic ushering in its endemic phase"

Public Health Agency of Canada. Omicron monitoring report. December 21, 2021.

-Canadian epidemiology - of those with available information, 2/1494 hospitalized, no deaths, and 71% of cases were fully vaccinated

Sheikh A, Kerr S, Woolhouse M, McMenemy J, Robertson C. Severity of Omicron variants of concern and vaccine effectiveness against symptomatic disease: national cohort with nested test negative design study in Scotland. Edinburgh Research Explorer [Preprint] 2021.

-using Scotland-wide EAVE II platform, a cohort analysis with a nested test negative design incident case control study from 1Nov-19Dec/21, adjusted for age, sex, SES, vaccination status, clinical risk factors; 23840 SGTF cases. Omicron risk of hospital admission: aRR 0.32 (0.19, 0.52)

Ulloa AC, Buchan SA, Daneman N, Brown KA. Early estimates of SARS-CoV-2 Omicron variant severity based on a matched cohort study, Ontario, Canada. medRxiv 2021.

<https://doi.org/10.1101/2021.12.24.21268382>.

-In Ontario, cases matched on gender, age, vaccination status, health region, onset date; 11622/29594 Omicron could be matched to Delta case (14181); 22Nov to 25Dec/21. Risk of hospitalization or death: HR 0.35 (0.26, 0.46) (0.51% were hospitalized), and ICU admission or death: HR 0.17 (0.08, 0.37) (0.03% deaths). Results were similar by age, gender, and vaccination status, and all indicated reduced severity of Omicron.

Meng B, Ferreira IATM, Abdullahi A, Saito A, Kimura I, Yamasoba D, et al. SARS-CoV-2 Omicron spike mediated immune escape, infectivity and cell-cell fusion. bioRxiv 2021.

<https://doi.org/10.1101/2021.12.17.473248>.

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-In Omicron, the observed cleavage efficiency [of the S-protein] is substantially lower; Omicron spike pseudotyped virus entry into lower airway organoids and Calu-3 lung cells was impaired; fusogenicity of Omicron BA.1 spike was severely impaired despite TMPRSS2 expression, leading to marked reduction in syncytium formation. Authors conclude that this indicated that suboptimal Omicron S1/S2 cleavage reduces efficient infection of lower airway cells expressing TMPRSS2, but not TMPRSS2 negative cells such as those found in the upper airway, likely explaining the reduced severity.

Wolter N, Jassat W, Walaza S, Welch R, Moultrie H, Groome M, et al. Early assessment of the clinical severity of the SARS-CoV-2 Omicron variant in South Africa. medRxiv 2021.

<https://doi.org/10.1101/2021.12.21.21268116>.

-In South Africa from 1Oct-30Nov/21, Omicron infections had lower odds of being admitted to hospital: aOR 0.2 (0.1, 0.3), and lower odds of severe disease: aOR 0.3 (0.2, 0.5).

The Genotype to Phenotype Japan (G2P-Japan) Consortium. Attenuated fusogenicity and pathogenicity of SARS-CoV-2 Omicron variant. Preprint. 2021.

-Omicron is more transmissible, but has attenuated pathogenicity - less fusogenic in cell culture, and S is faintly cleaved.

Wang L, Berger NA, Kaelber DC, Davis PB, Volkow ND, Xu R. COVID infection severity in children under 5 years old before and after Omicron emergence in the US. medRxiv 2022.

<https://doi.org/10.1101/2022.01.12.22269179>.

-In 7201 infected between 12/26/21 to 1/6/22, after propensity-score matching for demographics, SE determinants of health, comorbidities, and medication, Omicron compared to Delta cohort: ED visits RR 0.71 (0.66, 0.75); hospitalizations RR 0.33 (0.26, 0.43); ICU admissions RR 0.32 (0.16, 0.66); and mechanical ventilation RR 0.29 (0.18, 0.46).

Lewnard JA, Hong VX, Patel MM, Kahn R, Lipsitch M, Tartof SY. Clinical outcomes among patients infected with Omicron (B.1.1.529) SARS-CoV-2 variant in southern California. medRxiv 2022.

<https://doi.org/10.1101/2022.01.11.22269045>.

-Kaiser Permanente Southern California healthcare system, from 30Nov/21 to 1Jan/22. Among cases first tested in outpatient settings, for Omicron compared to Delta, aHR hospital admission 0.48 (0.36, 0.64); aHR symptomatic hospital admission 0.47 (0.35, 0.62); HR ICU admission 0.26 (0.10, 0.73); HR mortality 0.09 (0.01, 0.75); median duration of hospital stay 3.4 (2.8, 4.1) days shorter [69.6% (64.0-74.5) reduction].

Davies MA, Kassanjee R, Rosseau P, Morden E, Johnson L, Solomon W, et al. Outcomes of laboratory-confirmed SARS-CoV-2 infection in the Omicron-driven fourth wave compared with previous waves in the Western Cape Province, South Africa. medRxiv 2022.

<https://doi.org/10.1101/2022.01.12.22269148>.

-In public sector patients age 20y+ from 14Nov-11/Dec/21 (and follow-up to 26Dec/21), adjusted for age, sex, comorbidities, geography, vaccination, and prior infection. Compared to Delta wave 3: aHR death 0.27 (0.19, 0.38), adjusted for vaccination and prior infection aHR 0.41 (0.29, 0.59), and attempt at adjusting for unascertained prior infections [assuming 15% ascertained, and natural immunity reduces risk by 70-80%] aHR 0.72. Similar reductions in severe hospitalization/death: 0.28 (0.22, 0.36), 0.43 (0.33, 0.55), 0.75.

Omicron has evaded vaccine efficacy for infection

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Discovery Health. Real-world data relating to Omicron experience critical to guiding global response. Johannesburg, South Africa. Press Release o 14 December 2021.

-data from the first 3 weeks of Omicron wave in South Africa [now accounts for 90% of new infection, with steeper trajectory of new infection], includes 211K positive tests. In a test-negative design VE: 2-dose Pfizer against hospitalization 70% [67% 60-69y, and 60% 70-79y], but against infection 33%, consistent against range of chronic illnesses [DM, HBP, hypercholesterolemia, CVD].

Adalja A. Don't jump the gun on boosting all adults. Let's focus on reaching the unvaccinated at home and abroad as we await more data on Omicron. MedPage Today. December 2, 2021.

-Discusses the following: we need to prioritize the global fight against COVID-19 [which depends on first and second doses]; with a destined to be endemic CoV, breakthrough infection is likely for most people, so the focus must be on the success of the vaccines at preventing what matters – serious illness, hospitalization, and death in the vulnerable; and the risk of 'original antigenic sin' [that explained patterns of severe illness during the 2009 H1N1 Influenza pandemic] from vaccines antigenically too far from the drifted Omicron variant.

Ferguson N, Ghani A, Cori A, Hogan A, Hinsley W, Volz E, on behalf of the Imperial College COVID-19 Response Team. Report 49: Growth, population distribution and immune escape of Omicron in England. December 16, 2021.

-between Nov 11 to Dec 11/21 in England, VE for symptomatic infection was between 0 and 20% after dose 2, and between 55% and 80% shortly after booster

Redd AD, Nardin A, Kared H, Bloch EM, Abel B, Pekosz A, et al. Minimal cross-over between mutations association with Omicron variants of SARS-CoV-2 and CD8+ T cell epitopes identified in COVID-19 convalescent individuals. bioRxiv 2021. <https://doi.org/10.1101/2021.12.06.471446>.

-in 30 convalescent individuals, virtually all individuals with existing anti-SARS-CoV-2 CD8+ T cell responses should recognize the Omicron VOC. This suggests that the T-cell immune response in previously infected should still be effective against Omicron [i.e., preventing severe disease].

Brandal LT, MacDonald E, Veneti L, Ravlo T, Lange H, Naseer U, et al. Outbreak caused by the SARS-CoV-2 Omicron variant in Norway, November to December 2021. Euro Surveill 2021;26(50):pii=2101147.

-Outbreak at a Christmas party at a restaurant in Oslo with 117 attendees (96% vaccinated, and had negative rapid antigen self-test within 1-2d of party) - attack rate 81 (74%), none hospitalized, 79 (98%) were fully vaccinated.

Andrews N, Stowe J, Kirsebom F, Toffa S, Rickeard T, Gallagher E, et al. Effectiveness of COVID-19 vaccines against the Omicron (B.1.1.529) variant of concern. medRxiv 2021. <https://doi.org/10.1101/2021.12.14.21267615>.

-a test-negative case-control design in England from 27Nov to 6Dec/21 with 581 Omicron cases to determine VE against symptomatic disease. For ChAdOx1 [AstraZeneca], no effect against Omicron from 15wk after 2nd dose; for BNT162b2 [Pfizer] VE 88.0% (65.9, 95.8) 2-9 weeks later, dropping to 34-37% from 15wk after 2nd dose. For BNT162b2 booster, 2 weeks after VE increased to 71.4% (41.8, 86.0) for initially ChAdOx1 vaccinated and 75.5% (56.1, 86.3) for initially BNT162b2 vaccinated, shortly after booster.

Hansen CH, Schelde AB, Moustsen-Helm IR, Emborg HD, Krause TG, Molbak K, et al. Vaccine effectiveness against SARS-CoV-2 infection with the Omicron or Delta variants following a two-dose or

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booster BNT162b2 or mRNA-1273 vaccination series: A Danish cohort study. medRxiv 2021.

<https://doi.org/10.1101/2021.12.20.21267966>.

-In Danish residents 12y+ from Nov20-Dec12/21, there was rapid waning over the course of 5 months, restored in the first month after booster dose.

VE	Pfizer		Moderna	
Time	Omicron	Delta	Omicron	Delta
1-30d	55.2% (23.5, 73.7)	86.7 (84.6, 88.6)	36.7 (-69.9, 76.4)	88.2 (83.1, 91.8)
31-60d	16.1 (-20.8, 41.7)	80.9 (79.0, 82.6)	30.0 (-41.3, 65.4)	81.5 (77.7, 84.6)
61-90d	9.8 (-10.0, 26.1)	72.8 (71.7, 73.8)	4.2 (-30.8, 29.8)	72.2 (70.4, 74.0)
91-150d	-76.5 (-95.3, -59.5)	53.8 (52.9, 54.6)	-39.3 (-61.6, -20.0)	65.0 (63.6, 66.3)
14-44d after booster	54.6 (30.4, 70.4)	81.2 (79.2, 82.9)	-	82.8 (58.8, 92.9)

Buchan SA, Chung H, Brown KA, Austin PC, Fell DB, Gubbay JB, et al. Effectiveness of COVID-19 vaccines against Omicron or Delta infection. medRxiv 2021.

<https://doi.org/10.1101/2021.12.30.21268565>.

-A test-negative design from 22Nov-19Dec/21 in Ontario in those age 18y+, adjusted for age, sex, region of residence, tests during 3mos prior to 14Dec/20, past infection, comorbidities, influenza vaccination, household income, non-essential workers, visible minority, persons per dwelling. Receipt of 2 doses of COVID-19 vaccines was not protective against Omicron [in fact, was negative VE: -38% (-61, -18) at 120-179d, -42% (-69, -19) at 180-239d], and VE against Omicron 37% (19, 50) 7d+ after mRNA third dose, and “the duration of this protection and effectiveness against severe disease are uncertain”.

Keeton R, Tincho MB, Ngomti A, Baguma R, Benede N, Suzuki A, et al. SARS-CoV-2 spike T cell responses induced upon vaccination or infection remain robust against Omicron. medRxiv 2021.

<https://doi.org/20.1101/2021.12.26.21268380>.

-70-80% of the CD4 and CD8 T cell response to spike was maintained; the magnitude of Omicron cross-reactive T cells was similar to that of the Beta and Delta variants; and there were comparable T cell responses to ancestral spike, nucleocapsid and membrane proteins to those found in patients hospitalized in previous waves dominated by the ancestral, Beta or Delta variants. This indicated well-preserved T cell immunity to Omicron that is likely to contribute to protection from severe COVID-19.

UK Health Security Agency. SARS-CoV-2 variants of concern and variants under investigation in England. Technical briefing: Update on hospitalization and vaccine effectiveness for Omicron VOICI-21Nov-01 (B.1.1.529). December 31, 2021.

-In the UK, the risk of presentation to emergency care or hospital admission with Omicron vs Delta was HR 0.53 (0.50, 0.57), the risk of hospitalization from ED was HR 0.33 (0.30, 0.37), and was also lower in school-aged children 5-17y compared to Delta: HR 0.42 (0.28, 0.63).

-In the UK, using a test-negative case-control design, and adjusted for age, gender, previous positive test, region, ethnicity, clinically extremely vulnerable status, risk group status, period, the VE against symptomatic disease was: for 2 doses AstraZeneca no effect from 20wk+; 2 doses Pfizer or Moderna by 20wk+ effect around 10%; after booster dose VE at 2-4wk 65-70%, 5-9wk 55-70%, and 10wk+ 40-50% [waning faster for Omicron than for Delta]. Hospitalization after 2 doses was less likely at 2-24wk HR 0.33 (0.21, 0.55), 25wk+ 0.49 (0.30, 0.81), and after booster 2wk+ 0.32 (0.18, 0.58) - protection much greater than against symptomatic disease. “Further data is needed to estimate the duration of protection against hospitalization.”

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UK Health Security Agency. SARS-CoV-2 variants of concern and variants under investigation in England. Technical briefing 34. 15 Jan, 2022.

-VE mild disease: largely disappeared by 20wk+ after 2 doses [for Pfizer or Moderna was around 10%]. Booster VE increases to 65-70% initially, but drops to 45-50% from 10wk+; VE hospitalization [combined with efficacy against symptomatic disease]: 2 doses 2-24wk 64% (54, 71), 25wk+ 44% (30, 54). Booster 92% 2-4wk, and remains at 83% (78, 87) 10wk+ after.

Willett BJ, Grove J, MacLean OA, Wilkie C, Logan N, De Lorenzo G, et al. The hyper-transmissible SARS-CoV-2 Omicron variant exhibits significant antigenic change, vaccine escape and a switch in cell entry mechanism. medRxiv 2022. <https://doi.org/10.1101/2022.01.03.21268111>.

-Found markedly reduced real-world VE after 2 doses, with partial recovery after 3rd dose mRNA booster, in a logistic additive model with a test negative case control design in 1.2M people in the largest health board in Scotland from 6-12Dec/21. Adjusted VE in recent recipients 2 doses: ChAdOx1 negative, BNT162b2 6.84%, mRNA-1273 8.83%; VE in recent booster dose: BNT162b2 67.57%, mRNA-1273 71.15%; VE overall where median time since most recent dose is 5mos: 2 doses ChAdOx1 5.19%, BNT162b2 24.39%, mRNA-1273 24.86%. Efficacy against severe disease is “likely to be more durable”.

Kuhlmann C, Claassen M, Maponga T, Sutherland AD, Suliman T, Shaw ML, Preiser W. Breakthrough infections is SARS-CoV-2 Omicron variant despite booster dose of mRNA vaccine. Available at: SSRN <http://dx.doi.org/10.2139/ssrn.3981711>.

-Describes a group of 7 German visitors in late November/early December 2021 to Cape Town, South Africa, who on arrival in November had negative PCR test and record of being fully vaccinated [5-10 months prior] including a booster mRNA dose [1-2 months prior]. All had mild or moderate symptoms from Omicron. The authors conclude that “even three doses of mRNA vaccines may not be sufficient to prevent infection and symptomatic disease with the Omicron variant.”

Prasad V. Vaccine effectiveness (against infection not severe disease) goes down the drain.

Plummeting VE changes health care policy. Substack. Jan 9, 2022. Available at:

<https://vinayprasadmdmph.substack.com/p/vaccine-effectiveness-goes-down-the?justPublished=true>

-Reviewing recent studies, discusses the following: 2 vaccine doses does nothing or almost nothing to stop symptomatic Omicron; 3 vaccine doses barely does anything, and the effect will likely attenuate over time; as the number of exposures increase, the cumulative probability of infection will approach 1; Conclusion – you cannot contain the viral spread of Omicron by boosting. Thus, argues that “booster mandates make no sense for young people/working people/hospitals/anywhere” and that “draconian avoidance of Omicron is not tenable. Omicron or a future variant will eventually find us all... It is time to face reality.”

Lyngse FP, Mortensen LH, Denwood MJ, Christiansen LE, Moler CH, Skov RL, et al. SARS-CoV-2 Omicron VOC transmission in Danish households. medRxiv 2021.

<https://doi.org/10.1101/2021.12.27.21286278>.

-Danish households during Dec 2021, Secondary Attack Rate (SAR) was 31% with Omicron [21% with Delta]. Comparing households infected with Omicron to Delta, the SAR was higher in unvaccinated 1.17 (0.99, 1.38), fully vaccinated 2.61 (2.34, 2.90), and 3.66 (2.65, 5.05) for booster-vaccinated. The rapid spread of Omicron “primarily can be ascribed to the immune evasiveness”.

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Tseng HF, Ackerson BK, Luo Y, Sy LS, Talarico CA, Tian Y, et al. Effectiveness of mRNA-1273 against SARS-CoV-2 omicron and delta variants. medRxiv 2022.

<https://doi.org/10.1101/2022.01.07.22268919>.

-A test negative study from Kaiser-Permanente Southern California, 12/6/21 to 12/23/21. Randomly sampled test negative controls matched 5:1 to cases by age, sex, race/ethnicity, specimen collection date. Two doses VE Omicron infection: 30.4% (5.0, 49.0) at 14-90 days, and declined rapidly thereafter, to 15.2% by 91-180 days, and 0% by 181-270 days. 2 hospitalized [and with one dose, none hospitalized]. Three dose VE Omicron infection: 62.5% (56.2, 67.9), none hospitalized, and in those boosted on or after 10/21/21 [median 36 days] 64.1%, but in those boosted on or prior to 10/20/21 [median 103 days] 49.0% [with 95% CI down to about 10%].

UK Health Security Agency. Press release. Boosters continue to provide high levels of protection against severe disease from Omicron in older adults. Jan 7, 2022.

-booster VE for hospitalization age 65+ at 3 mos about 90% [VE mild symptomatic was at 3 mos around 30%]; compared to 2 doses VE against severe disease at 3 mos 70% and at 6mos 50%

UKHSA. Effectiveness of 3 doses of COVID-19 vaccines against symptomatic COVID-19 and hospitalization in adults aged 65 years and older.

-test-negative case-control design, community testing, 27Nov-31Dec/21, adjusted for age, gender, previous positive test, region, clinically extremely vulnerable, risk group status, recent travel, period. The VE for mild disease 20wk+ was minimal or no effect, and after booster 2-4wk 62-65%, 5-9wk 48-56%, 10+wk 32%. The VE for hospitalization, for booster at 2-9wk 89%, 10wk+ 85%, but no data was provided for VE of 2-doses.

Andrews N, Stowe J, Kirsebom F, Toffa S, Rickeard T, Gallagher E, et al. Effectiveness of COVID-19 vaccines against the Omicron (B.1.1.529) variant of concern. medRxiv 2021.

<https://doi.org/10.1101/2021/12.14.21267615>.

-test-negative case-control design, 27Nov-6Dec/21 [before Omicron]. The VE for symptomatic disease and 2 ChAdOx1 doses 15wk+ no effect, and 2 BNT162b2 doses 2-9wk 88% and at 15wk+ 34-37%. The VE booster for symptomatic disease was at 2wk+ 88% (65.9, 95.8) and 75.5% (56.1, 86.3) respectively.

Andrews N, Stowe J, Kirsebom F, Toffa S, Sachdeva R, Gower C, et al. Effectiveness of BNT162b2 (Comirnaty, Pfizer-BioNTech) COVID-19 booster vaccine against COVID-19 related symptoms and hospitalization in England: test negative case-control study. medRxiv 2021.

-UK booster doses introduced 14Sept/21; symptomatic adults age 50+ from samples 13Sept/21 with follow-up to 5Nov/21; adjusted for age, sex, index of multiple deprivation, ethnic group, care home residence, region, period, HCW, social care worker, clinical risk group, clinically extremely vulnerable, severely immunosuppressed, previously testing positive

VE (% with 95%CI) Pre-Omicron	2 doses		Booster with Pfizer	
	AstraZeneca	Pfizer-BioNTech	AstraZeneca	Pfizer-BioNTech
Symptomatic	43.7% (41.9, 45.4)	63.4% (62.1, 64.6)	93.8 (93.3, 94.3)	94.3 (93.9, 94.6)
Hospitalization	89.5% (88.1, 90.7)	93.1% (92.0, 94.0)	98.8% (97.4 99.5)	98.8% (98.1, 99.2)

-“at least in the short-term... not yet clear how long protection against COVID-19 following booster vaccination will last”

El Gato Malo. Bayesian datacrime: Defining vaccine efficacy into existence. Stats with Cats, Substack. Jan 12, 2022. <https://boriquagato.substack.com/p/bayesian-datacrime-defining-vaccine>

-Points out several biases in the observational vaccine effectiveness studies.

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1. Studies don't count vaccinated (or boosted) as vaccinated (or boosted) until 2 weeks after the shot - so you get apparent VE where there is none, because cases in those 2 weeks are shifted to the unvaccinated (or un-boosted) cohort.
 2. The faster vaccine or booster is ramped up, the worse it makes unvaccinated or un-boosted seem - you are not accounting for cohort size properly, because you are "counting 'boosted today' vs 'cases reported in those boosted 14d+ ago'", i.e., inflating the boosted denominator. This results in "strong predictable bias toward making whatever group was vaxxed most recently look like vaccine is working", and that apparent efficacy fades as the growth in their group slows.
 3. The vaccines may trigger a ~2wk window of immune suppression - if vaccinated people get sick they are not counted as a booster illness but rather as a double-vaxxed illness; this can change a product that increases risk and make it look effective, and favor whatever group become 'fully vaxxed' most recently.
 4. Sequential selection effects – those who manage to get to 2 or 3 doses without catching Covid are already sorted to be the strongest, leaving only the best immune systems in the 'boosted but never sick' group. Moreover, if those who get vaxxed have short-term higher risk, and after they recover, they stay in the vaxxed or booster groups, that leaves those groups with higher immunity overall.
- Overall, this is why RCTs are used, to "get the bias out and equalized before you start". But the RCTs were ended far too early, and had other severe weaknesses.

El Gato Malo. Vaccine efficacy and social duty. Have we created a prisoner's dilemma? Jan 14, 2022.

<https://boriquagato.substack.com/p/vaccine-efficacy-and-social-duty>

1. Vaccines were first sold to us as a social duty: get the jab, stop the spread ["it's not about you, it's about all of us"]. But vaccines are non-sterilizing, do not stop infection, carriage, or transmission.
2. The vaccine debate then shifted away from cases onto 'severity': the unvaccinated will clog hospitals and harm society, so you must vaxx to protect access to medical care. But there are problems:
 - a. If vaccines reduce risk of death by 50% but have negative efficacy for cases, that might put you right back to where you started, and you also increased your risk of spreading the virus. An example [modified from the post] - suppose vaccine reduces risk of hospitalization 60%, but increases risk of infection 60%, so that my vaccine means 60% increased risk of infection and 60% reduced risk of hospitalization for me [my risk of hospitalization is about the same], but my risk of spreading has gone up 60%, so that my vaxxed contacts have 60% increased exposure risk, 60% increased infection risk, and 60% reduced risk of hospitalization = $1.6 \times 1.6 \times 0.6 = 1.54X$ risk of hospitalization. A classic Prisoner's Dilemma - the best course of action is to have trust, forego self-interest, and both stay unvaxxed.

Risk of hospitalization	B not vaxxed	B vaxxed
A not vaxxed	1X	0.6X B; 1.6X A
A vaxxed	0.6X A, 1.6X B	Both 1.54X risk

3. Places with higher vaxx rates should be showing strong signals overall on reduced hospitalizations - but they are not. Bremen is highest vaxxed (almost 100%) in Germany but has highest cases/100K in last 7d and highest hospitalization rate in Germany [with hardly any difference between 2021 and 2022]; Vermont is most vaxxed state, and adjusting for testing rate, cases there are up 342%, and hospitalization up 137%, higher than rates last year.

-Vaccines and boosters associated with faster case growth in UK. Especially among the oldest and highest risk. This is a worrying trend. Jan 18, 2022.

-New data on vaccine efficacy from Scotland and more evidence on Bayesian datacrime. And more bad news for "the experts." Jan 19, 2022.

-Discusses that the risk ratio for cases [cases-per-100K vaxxed / cases-per-100K unvaxxed] was over 1 in all ages in the UK and Scotland in January (meaning higher case-rates in the 2-dose vaccinated); the risk ratio for hospitalization was over 1 in Scotland in January (meaning higher hospitalization rates in the 2-dose vaccinated); the risk ratio for growth rate of cases from

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December to January in UK was over 1 for all age groups (and over 2.5 for age 70y+) (meaning more rapid growth in cases in the 2-dose vaccinated). This crude data supports the possibility of original antigenic sin with previous vaccination and Omicron, and of a prisoner's dilemma having occurred.

Doidge N. Vaccines are a tool, not a silver bullet. If we'd allowed more scientific debate, we would have realized this earlier. Globe and Mail. Jan 22, 2022.

-Discusses several important points. 1. The master narrative was wrong [that "Public Health would stop the spread with extemporizing measures such as lockdowns, discouraging social functions and travel, and closing schools and businesses until the vaccine arrived, all of which would protect us until we achieved vaccine-induced herd immunity everywhere, which, we were told, would eliminate the virus." 2. The military metaphor was harmful [that the "master narrative was our battle plan and this was a 'war' to eradicate the enemy virus... Scientists were to be soldiers in this new army... [But] the kind of virtues that may suit soldiers in an army (following an authority without questioning) are vices in science, which is a mode of critical inquiry..."]. 3. Vaccines are not the answer - a) two-dose VE dropped and became negative against Omicron, with equal transmission; b) booster may protect from severe disease but [in Denmark] 'only to those over 70 years', c) booster infection VE dropped in [UK] to 45% at only 10 weeks, and in [ON] was 37% at >7d, with ongoing safety concerns; c) RCTs were not designed to detect reduction in any serious outcome [hospital admission, ICU, death] or transmission, and looked at vaccines at their most potent [2 months] in a low-risk population [4.4% >75y]; d) more and more people in severe/critical condition were immunized, and e) have been silent about natural immunity [likely present in a majority of the unvaccinated]. Overall, herd immunity is unreachable, eradication is impossible, and "our COVID mandates have decoupled from the science originally used to justify them... [we need] a new plan – to live with the virus and get back to living a normal life..."

Comment on indications for Booster Doses: an argument

1. Omicron is now the most prevalent variant and has markedly lower severe outcomes: even adjusted for vaccination status, with reduced risk of hospitalization at least in half, and reduced risk of death even more.
2. VE of 2 doses against hospitalization may still be high: in the UK, for Omicron, in those age 65+ at least 50-70% protection against severe disease after 3-6 months [while 1.5mos+ after booster was 85%]; prior to Omicron, from 13Sept/21 VE for hospitalization at 140+ days after dose 2 was 89.5% for AstraZeneca and 93.1% Pfizer-BioNTech, and 14+ days after booster dose was 98.8%. These data suggest the *incremental benefit* of a booster for hospitalization may be up to 10-20% efficacy.
3. Conclusion: not having a booster dose is not driving the pandemic or hospitalizations, even in older age groups.