I hope your week is going well so far.

Today the “big” news is the expected approval in vaccinating children ages 12-15 next week by the FDA. See my comments

Under Journal Review I continue to try and find articles across several specialties. The first article is to my knowledge the first review on lung transplants for severe SARS-CoV-2. The next two articles highlight what many of us already know, this pandemic has disproportionately impacted minority and ethnic groups. The last article demonstrates the impact of the P.1 variant in Brazil which ties back to my comments about vaccinations in the COVID-19 News section.

Have a great day

Ed

COVID-19 News

FDA to Authorize Pfizer Vaccine for Adolescents by Early Next Week
The Food and Drug Administration is preparing to authorize use of the Pfizer vaccine in adolescents 12 to 15 years old as early next week. If it is granted, the CDC’s vaccine advisory panel is likely to meet the following day to review the clinical trial data and make recommendations for the vaccine’s use in adolescents. This is welcome news to parents who are anxious to protect their children during summer activities and before the start of the next school year. Vaccinating children is key to increasing the level of immunity and decreasing transmission.

Pfizer reported several weeks ago that none of the adolescents in the clinical trial who received the vaccine developed symptomatic infections. The company said that volunteers produced strong antibody responses and experienced about the same side effects seen in people ages 16 to 25.

Comment: This is certainly good news. However, there is a stark contrast in vaccinations between rich and poor countries. From Asia to Africa to Latin America — suffering is more than ever. Globally, there are more than 900,000 new cases a day. India's Covid-19 total has topped 20 million. Daily cases in India have surpassed 300,000 for 14 days in a row, evolving into the worst surge of the pandemic. While 44% of all Americans have received at least one dose of vaccine, countries that are experiencing serious outbreaks have much lower vaccination percentages: Canada 34%, Sweden 25%, Turkey 16%, Brazil 14%, Mexico 10%, India 9%, and Peru 3% to name a few. Use in adolescents raises questions about whether the current supply should be targeted to an age group that so far appears to be mostly spared from severe Covid-19.

Stopping surges elsewhere would also serve not only the U.S. interests, but the world. Uncontrolled spread of the virus can select for variants, which can come to the U.S. and elsewhere and already has. A few current examples: the Brazilian P1 variant and the UK B.1.1.7 both are more transmissible than wild type virus, and therefore spread more rapidly. There are new worries about the B.1.617 variant spreading rapidly in India. New variants may eventually evade vaccines and could set the world back in our fight to contain SARS-CoV-2.

Today, more than 148 million Americans have received at least one dose, and more than 105 million are fully vaccinated. The U.S. should encourage Pfizer, Moderna, and Johnson & Johnson to export Covid-19 vaccines using Covax prioritizing countries based on their Covid-19 death tolls and stress on their health care systems. The need is especially great now in India, Central and South America, and Mongolia. Do not get me wrong, I strongly support vaccinating our children 12-15 when the FDA approves EUA hopefully in the next 1-2 weeks, but we can save millions of people's lives overseas now by getting them vaccinated without compromising our own safety and security. I personally think we have a moral obligation to do so.

Journal Review

Early Outcomes After Lung Transplantation for Severe COVID-19: A Series of the First Consecutive Cases from Four Countries

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The authors established a multi-institutional case series that included the first consecutive transplants for severe COVID-19-associated ARDS known to us in the USA, Italy, Austria, and India including information relating to patient demographics and pre-COVID-19 characteristics, pre-transplantation disease course, perioperative challenges, pathology of explanted lungs, and post-transplantation outcomes.

Between May 1 and Sept 30, 2020, 12 patients with COVID-19-associated ARDS underwent bilateral lung transplantation at six high-volume transplant centers in the USA (eight recipients), Italy (two recipients at one center), Austria (one recipient), and India (one recipient). The median age of recipients was 48 years (IQR 41–51); three of the 12 patients were female. Chest imaging before transplantation showed severe lung damage that did not improve despite prolonged mechanical ventilation and extracorporeal membrane oxygenation. The lung transplant procedure was technically challenging, with severe pleural adhesions, hilar lymphadenopathy, and increased intraoperative transfusion requirements. Pathology of the explanted lungs showed extensive, ongoing acute lung injury with features of lung fibrosis. There was no recurrence of SARS-CoV-2 in the allografts.

Panel: Proposed criteria for the selection of patients with severe COVID-19 for lung transplantation

General criteria

- Age younger than 65 years, extended to younger than 70 years in exceptionally fit individuals
- Single-organ failure; in selected cases, multiorgan transplantation can be considered
- No malignancy or disabling comorbidities
- No dependence (alcohol, drugs, other) and not an active smoker
- Body-mass index in the range of 17–32 kg/m², with exceptions on a case-by-case basis
- Postoperative social support available (at least one reliable primary and one secondary caregiver identified)
- Insurance approval obtained or financial support established for transplant-related care, as applicable
- Patient and caregivers agreeable to lung transplantation and willing to relocate close to the transplantation centre for a period established by the transplantation centre

Neurocognitive status

- Patient is awake and interactive, with exceptions in selected cases if sedation wean is associated with severe hypoxaemia and haemodynamic changes
- If not awake and interactive, evidence supporting the absence of irreversible brain injury is obtained through physical assessment and brain imaging or neuropsychological consultation; an individual with medical power of attorney is identified who can make informed decisions consistent with patient's goals and consent to transplantation

General condition

- Patient is participating in physical therapy while hospitalised; exceptions can be made in selected cases if transplant evaluation is urgent, the patient has a high potential for post-transplantation recovery, and rehabilitation is hindered mainly due to lung injury associated with severe COVID-19

COVID-19 status

- Two negative PCR tests of bronchoalveolar lavage fluid are obtained, 24 h apart; in such cases, transplantation can be considered regardless of nasopharyngeal swabs when at least 4 weeks have elapsed since COVID-19 symptom onset, although both might be requested in some patients with a pre-existing immunosuppressive state, owing to concerns of prolonged shedding of replication-competent virus
- If separated from the ventilator with no tracheostomy, two negative PCR tests of nasopharyngeal swabs are obtained, 24 h apart
- When available, viral cultures are negative, confirming the absence of replication-competent virus in the potential transplant recipient; bronchoalveolar lavage should be used, when possible

Evidence of irreversible lung damage

- At least 4 weeks have elapsed since the onset of severe acute respiratory distress syndrome; rarely, evaluation for lung transplantation can be considered earlier than 4 weeks if potentially lethal pulmonary complications develop that cannot be managed medically or through the use of extracorporeal membrane oxygenation
- Lung recovery is deemed unlikely by at least two physicians from two different specialties (surgery, critical care, or pulmonary medicine), despite optimised medical care; transplantation should not be considered if ongoing lung improvement is seen, regardless of the time elapsed

Comment: Many of us have seen patients with irreversible ARDS who we believed had extensive fibrosis on ventilators for weeks on end. The evidence in this article shows that lung transplantation is feasible in patients with irreversible lung injury associated with COVID-19 who are un-weanable from mechanical ventilation or ECMO. The authors show, for the first time, that short-term post-transplantation outcomes can be achieved that are similar to those of transplant recipients without COVID-19. Candidate selection and the timing of and approach to lung transplantation is critical. [see above] They propose that patients considered for lung transplantation for severe COVID-19 should preferably be younger than 65 years, have no or manageable preexisting comorbidities, and have lung injury from which they are unlikely to survive without lung transplantation—a decision made in a multidisciplinary manner. They propose that all patients undergo double-lung transplantation. Lung transplantation should be considered only when sufficient time has elapsed since the onset of ARDS and lung recovery is deemed unlikely. They suggest that at least 4-6 weeks be allowed after the onset of ARDS before considering lung transplantation. They were concerned about ongoing infection at the time of transplantation and re-infection of the allograft. Accordingly, they did multiple bronchoscopic sampling of the lungs before transplantation and tested them for SARS-CoV-2 using PCR. Reassuringly, they did <u>not</u> detect viral transcripts or nosocomial pathogens after the transplantation. These observations agree with prior studies suggesting that it is rare to detect replicating virus more than 10 days after infection

with SARS-CoV-2 for routine cases and up to 20 days for severe cases, although the PCR result can remain positive for several weeks beyond infectivity. Unfortunately, there are not enough lungs available to transplant all patients who meet the criteria discussed in this publication.

Ethnic Differences in SARS-CoV-2 Infection and COVID-19-related Hospitalisation, Intensive Care Unit Admission, and Death in 17 Million Adults in England: An Observational Cohort Study Using the OpenSAFELY Platform

Lancet published online April 30, 2021
doi.org/10.1016/ S0140-6736(21)00949-1

The investigators conducted an observational cohort study of adults (aged ≥18 years) registered with primary care practices in England for whom electronic health records were available through the OpenSAFELY platform, and who had at least 1 year of continuous registration at the start of each study period (Feb 1 to Aug 3, 2020 [wave 1], and Sept 1 to Dec 31, 2020 [wave 2]). Outcomes of interest included SARS-CoV-2 testing and positive test results and COVID-19-related hospital admissions, intensive care unit (ICU) admissions, and death. Ethnicity was captured on the primary care record, grouped into five high-level census categories (White, South Asian, Black, other, and mixed) and 16 subcategories across these five categories, as well as an unknown ethnicity category. Models were adjusted for age, sex, deprivation, clinical factors and comorbidities, and household size, with stratification by geographical region.

17,288,532 adults were included in the study. 10,877,978 (62·9%) were White, 1,025,319 (5·9%) were South Asian, 340,912 (2·0%) were Black, 170,484 (1·0%) were of mixed ethnicity, 320 788 (1·9%) were of other ethnicity, and 4,553,051 (26·3%) were of unknown ethnicity. In wave 1, the likelihood of being tested for SARS-CoV-2 infection was slightly higher in the South Asian group (adjusted hazard ratio 1·08 [95% CI 1·07–1·09]), Black group (1·08 [1·06–1·09]), and mixed ethnicity group (1·04 [1·02–1·05]) and was decreased in the other ethnicity group (0·77 [0·76–0·78]) relative to the White group. The risk of testing positive for SARS-CoV-2 infection was higher in the South Asian group (1·99 [1·94–2·04]), Black group (1·69 [1·62–1·77]), mixed ethnicity group (1·49 [1·39–1·59]), and other ethnicity group (1·20 [1·14–1·28]). Compared with the White group, the four remaining high-level ethnic groups had an increased risk of COVID-19-related hospitalization (South Asian group 1·48 [1·41–1·55], Black group 1·78 [1·67–1·90], mixed ethnicity group 1·63 [1·45–1·83], other ethnicity group 1·54 [1·41–1·69]), and COVID-19-related ICU admission (2·18 [1·92–2·48], 3·12 [2·65–3·67], 2·96 [2·26–3·87], 3·18 [2·58–3·93]), and death (1·26 [1·15–1·37], 1·51 [1·31–1·71], 1·41 [1·11–1·81], 1·22 [1·00–1·48]). In wave 2, the risks of hospitalization, ICU admission, and death relative to the White group were increased in the South Asian group but attenuated for the Black group. Compared with these risks in white group were increased in the South Asian group but attenuated for the Black group compared with these risks in wave 1.

A Admitted to hospital for COVID-19

	Wave 1			Wave 2		
	Denominator	Events	HR (95% CI)	Denominator	Events	HR (95% CI)
All White ethnicities*	**11110312**	**20504 (0·2%)**	**1 (ref)**	**11323083**	**12120 (0·1%)**	**1 (ref)**
White British*	9683276	18627 (0·2%)	1 (ref)	9845315	11209 (0·1%)	1 (ref)
White Irish	79945	257 (0·3%)	1·14 (1·00–1·29)	81185	92 (0·1%)	0·94 (0·77–1·16)
Other White	1347091	1620 (0·1%)	1·04 (0·99–1·10)	1396583	819 (0·1%)	1·01 (0·94–1·09)
All South Asian ethnicities	**1026551**	**2836 (0·3%)**	**1·48 (1·41–1·55)**	**1061336**	**2100 (0·2%)**	**1·89 (1·79–2·00)**
Indian	432760	1179 (0·3%)	1·41 (1·32–1·50)	447812	665 (0·1%)	1·57 (1·44–1·71)
Pakistani	300528	924 (0·3%)	1·48 (1·38–1·59)	309214	992 (0·3%)	2·13 (1·98–2·30)
Bangladeshi	70395	153 (0·2%)	1·21 (1·03–1·42)	73154	151 (0·2%)	2·31 (1·96–2·72)
Other South Asian	222868	580 (0·3%)	1·85 (1·70–2·02)	231156	292 (0·1%)	1·94 (1·72–2·19)
All Black ethnicities	**342561**	**1051 (0·3%)**	**1·78 (1·67–1·90)**	**355625**	**362 (0·1%)**	**1·23 (1·11–1·37)**
Caribbean	83042	393 (0·5%)	1·58 (1·43–1·75)	84219	117 (0·1%)	0·98 (0·81–1·17)
African	190395	499 (0·3%)	2·10 (1·91–2·30)	199012	177 (0·1%)	1·44 (1·24–1·68)
Other Black	69124	159 (0·2%)	1·63 (1·39–1·90)	72394	68 (0·1%)	1·34 (1·05–1·70)
All mixed ethnicities	**171933**	**302 (0·2%)**	**1·63 (1·45–1·83)**	**179557**	**132 (0·1%)**	**1·33 (1·12–1·58)**
White and Caribbean	39631	79 (0·2%)	1·43 (1·14–1·78)	41228	39 (0·1%)	1·27 (0·92–1·74)
White and African	33438	65 (0·2%)	1·86 (1·46–2·38)	34991	21 (0·1%)	1·10 (0·72–1·69)
White and Asian	34629	63 (0·2%)	1·98 (1·55–2·54)	36257	34 (0·1%)	1·88 (1·34–2·64)
Other mixed ethnicity	64235	95 (0·1%)	1·55 (1·27–1·90)	67081	38 (0·1%)	1·23 (0·89–1·69)
All other ethnicities	**323529**	**504 (0·2%)**	**1·54 (1·41–1·69)**	**334962**	**222 (0·1%)**	**1·32 (1·16–1·51)**
Chinese	104560	70 (0·1%)	0·97 (0·77–1·23)	105658	20 (<0·1%)	0·53 (0·34–0·82)
All other ethnic groups	218969	434 (0·2%)	1·74 (1·58–1·91)	229304	202 (0·1%)	1·56 (1·35–1·79)
Unknown ethnicity	**4408386**	**7276 (0·2%)**	**1·06 (1·03–1·09)**	**4381803**	**3919 (0·1%)**	**1·07 (1·03–1·11)**

Comment: As other studies have shown, **"**the risks of SARS-CoV-2 infection and severe COVID-19 outcomes are disproportionately increased in minority ethnic groups, both in the UK and internationally. Reducing ethnic inequalities in COVID-19 risks requires action on social determinants including addressing disadvantage and discrimination, reducing risk of infection and transmission, improving quality of and access to quality clinical care, and improving management of pre-existing clinical conditions".

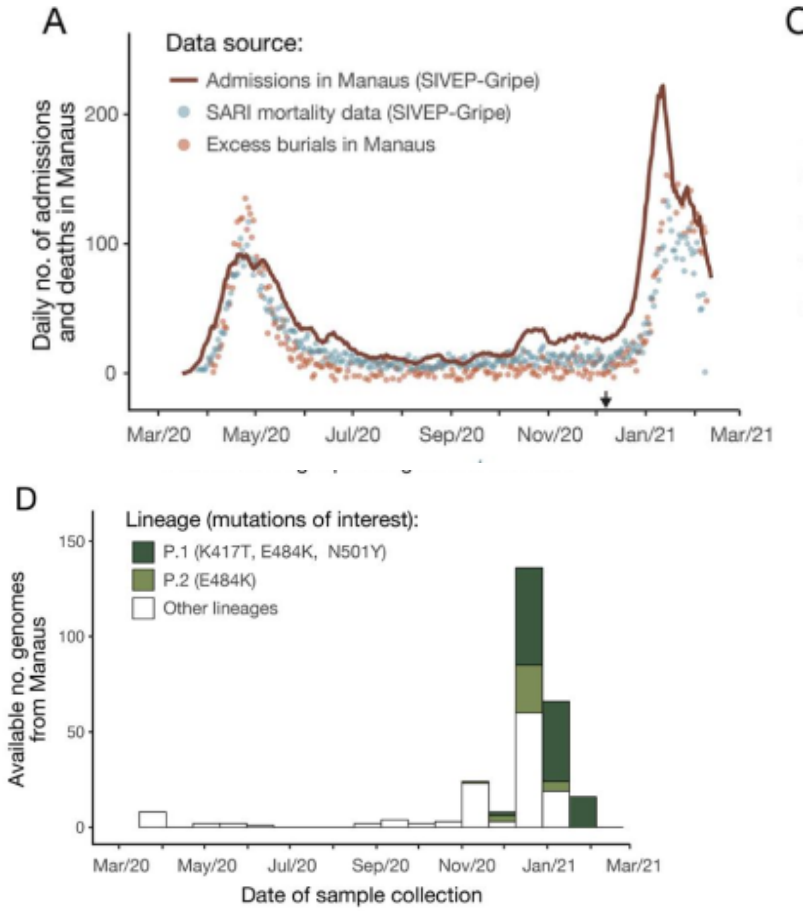
Association Between Income Inequality and County-Level COVID-19 Cases and Deaths in the US
JAMA Netw Open published online May 3, 2021
doi:10.1001/jamanetworkopen.2021.8799
The investigators evaluated the association between county-level income inequality and COVID-19 cases and deaths from March 2020 through February 2021. They used longitudinal data on county-level COVID-19 cases and deaths in 3220 counties from all 50 states, Puerto Rico, and the District of Columbia. They used the Gini coefficient, a measure of unequal income distribution (presented as a value between 0 and 1, where 0 represents a perfectly equal geographical region where all income is equally shared and 1 represents a perfectly unequal society).

There was a positive correlation between Gini coefficients and county-level COVID-19 cases (Spearman $\rho = 0.052$; $P < .001$) and deaths (Spearman $\rho = 0.134$; $P < .001$) during the study period. The association between income inequality and COVID-19 cases and deaths varied over time and was strongest in the summer months of 2020.

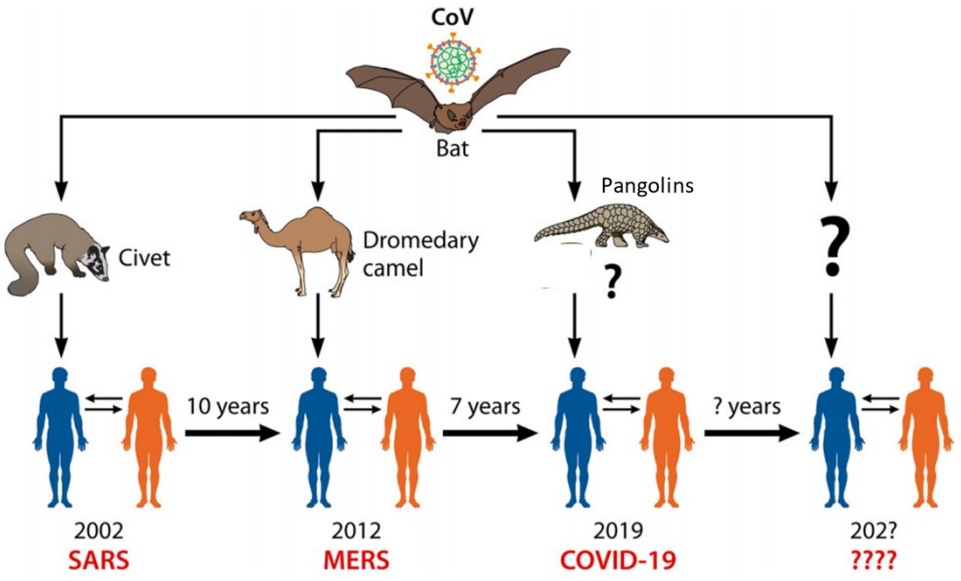
Comment: This study and others suggest that income inequality within US counties was associated with more cases and deaths due to COVID-19. They did not account for concurrent changes in measures of income and employment owing to the time-lag availability of these measures in the American Community Survey. In addition, they could have performed other forms of analysis, such as a time-series analysis, which would evaluate month-to-month changes and because some counties had small numbers of cases and death. Nonetheless, the COVID-19 pandemic has highlighted the disparities that

exist in health outcomes owing to income inequality in the US. We need to focus on areas of income inequality to flatten the curve but try to lessen the burden of inequality.

Genomics and Epidemiology of the P.1 SARS-CoV-2 Lineage in Manaus, Brazil
Science published online April 14, 2021
Doi:10.1126/science.abh2644
Cases of SARS-CoV-2 resurged in late 2020, despite prior high levels of infection in Manaus Brazil. Genome sequences were performed on viruses isolated between November 2020 and January 2021. This revealed a novel variant. Lineage P.1 acquired 17 mutations including a trio of spike proteins K417T, E484K, and N501Y which was associated with increased binding to the human ACE2 receptor. Using a two-category dynamical model that integrates genomic and mortality data, they estimate that P.1 may be 1.7-2.4-fold more transmissible, and that previous (non-P.1) infection provides 54-79% of the protection against infection with P.1 that it provides against non-P.1 lineages.



Comment: Global genomic surveillance is critical to pandemic surveillance response in the future. We must invest in our public health infrastructure globally so we can be better prepared for the next emerging infectious disease. **It is not a matter of if, it is a matter of when!** [see below]



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