Good morning and TGIF

In today's news I report the current incidence of influenza and other respiratory viruses. The "big" [but not a surprise] is the approval by the FDA Advisory Committee on the Moderna vaccine.

In terms of new publications, I have chosen an article which contrasts influenza with COVID-19 in hospitalized patients. The next article looks at the development of a metapopulation susceptible–exposed–infectious–removed (SEIR) model that integrates fine-grained, dynamic mobility networks to simulate the spread of SARS-CoV-2 in ten of the largest US metropolitan areas to guide reopening and shutdowns. The third study is a timely publication which provides an evidence base for global, regional, and national vaccine prioritization and allocation. [We sometimes forget we are not the only country impacted by SARS-CoV-2] The last article reminds us what we believed before about the relative low risk of Covid-19 among younger adults has simply not been borne out by emerging data.

Monday I will review two articles just published last PM in the NEJM on tocilizumab and monoclonal antibodies. There was not enough time for me to adequately review for today's Daily Briefing.

Stay safe and have a wonderful weekend.

Ed

COVID-19 News

Influenza and Other Respiratory Viruses
U.S. laboratories are finding significantly fewer flu cases among tested patients so far this year, compared with previous flu seasons. Between mask wearing, social distancing, and measures such as bar closures, this may also be impacting influenza. Clinical laboratories tested 22,474 patient samples, mostly nasal swabs, for influenza during the week ended Dec. 5, and only 40, or 0.2%, came back positive, according to data from the CDC. During the same period last year, more than 11% of over 41,000 samples were positive. In the Southern Hemisphere, Covid-19 precautions practically wiped out the flu this year (see below), offering hope for a lighter flu season in the U.S. and Europe.

Chile's influenza cases during flu season
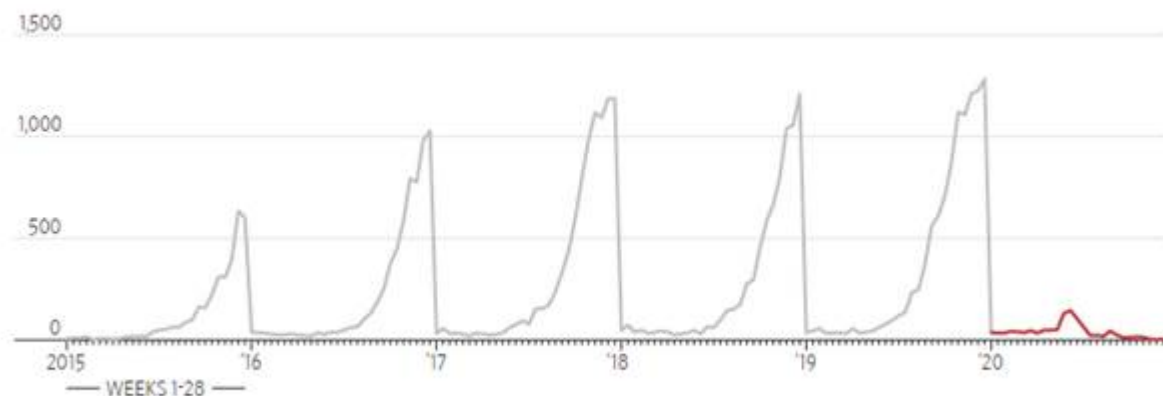
Source: Chile's Public Health Institute

Other seasonal viruses have also much lower this year. In September through November of 2019, Children's Health saw 892 cases of RSV, a common respiratory virus that usually infects children. During that same period in 2020, the system reported a single case. This is remarkably similar to what we saw in 2009 with H1N1.

FDA Advisory Committee Moderna COVID-19 Vaccine
The Vaccines and Related Biological Products Advisory Committee panel voted 20-0 on this question: "Based on the totality of scientific evidence available, do the benefits of the Moderna COVID-19 Vaccine outweigh its risks for use in individuals 18 years of age and older?" There was one abstention. Study data indicate the primary efficacy endpoint demonstrated vaccine efficacy (VE) of 94.1% (95% CI, 89.3% - 96.8%) for the Moderna vaccine, with 11 COVID-19 cases in the vaccine group and 185 COVID-19 cases in the placebo group. Moderna has said that the most common adverse reactions seen to date with its vaccine include injection site pain (88.2%), erythema (8.6%), swelling (12.2%), and ipsilateral lymphadenopathy (14.2%). The company has proposed a regimen of having its vaccine administered in two doses, 28 days apart. There is the suggestion the vaccine may also prevent transmission. FDA is expected to authorize EUA today.

Journal Reviews

Comparative Evaluation of Clinical Manifestations and Risk of Death in Patients Admitted to Hospital with COVID-19 and Seasonal Influenza: Cohort Study
BMJ published online November 2020
doi.org/10.1136/bmj.m4677
The investigators set out to examine differences in risk of clinical manifestations and death among people admitted to hospital with COVID-19 and seasonal influenza. They leveraged the electronic healthcare databases of the US Department of Veterans Affairs (VA), which operates the largest nationally integrated healthcare delivery system in the US, to do a comparative evaluation of clinical manifestations and outcomes among US veterans admitted to hospital with COVID-19 and seasonal influenza. Patients admitted to hospital with COVID-19 between 1 February 2020 and 17 June 2020 (n=3641) and seasonal influenza between 2017 and 2019 (n=12 676) were included. Risks of clinical manifestations, healthcare resource use (including use of mechanical ventilation, admission to intensive care, and length of stay), and death, estimated using a doubly robust approach to build propensity scores that were then used along with covariates to adjust the outcome models.

Compared with seasonal influenza, COVID-19 was associated with higher risk of acute kidney injury (odds ratio 1.52, 95% confidence interval 1.37 to 1.69), incident renal replacement therapy (4.11, 3.13 to 5.40), insulin use (1.86, 1.62 to 2.14), septic shock (4.04, 3.38 to 4.83), vasopressor use (3.95, 3.46 to 4.51), pulmonary embolism (1.50, 1.18 to 1.90), deep venous thrombosis (1.50, 1.20 to 1.88), stroke (1.62, 1.17 to 2.24), acute myocarditis (7.82, 3.53 to 17.36), arrythmias and sudden cardiac death (1.76, 1.40 to 2.20), elevated troponin (1.75, 1.50 to 2.05), elevated aspartate aminotransferase (3.16, 2.91 to 3.43), elevated alanine aminotransferase (2.65, 2.43 to 2.88), and rhabdomyolysis (1.84, 1.54 to 2.18). Compared with seasonal influenza, COVID-19 was also associated with higher risk of death, mechanical ventilator use, and admission to intensive care (hazard ratio 4.97, (95% confidence interval 4.42 to 5.58), 4.01 (3.53 to 4.54), and 2.41 (2.25 to 2.59), respectively) and 3.00 (2.20 to 3.80) additional days of hospital stay. Differences in rates of death per 100 patients between COVID-19 and seasonal influenza

were most pronounced in people over 75 years of age with chronic kidney disease or dementia and those with black race and obesity, diabetes, or chronic kidney disease.

Death

Mechanical ventilator use

Admission to intensive care
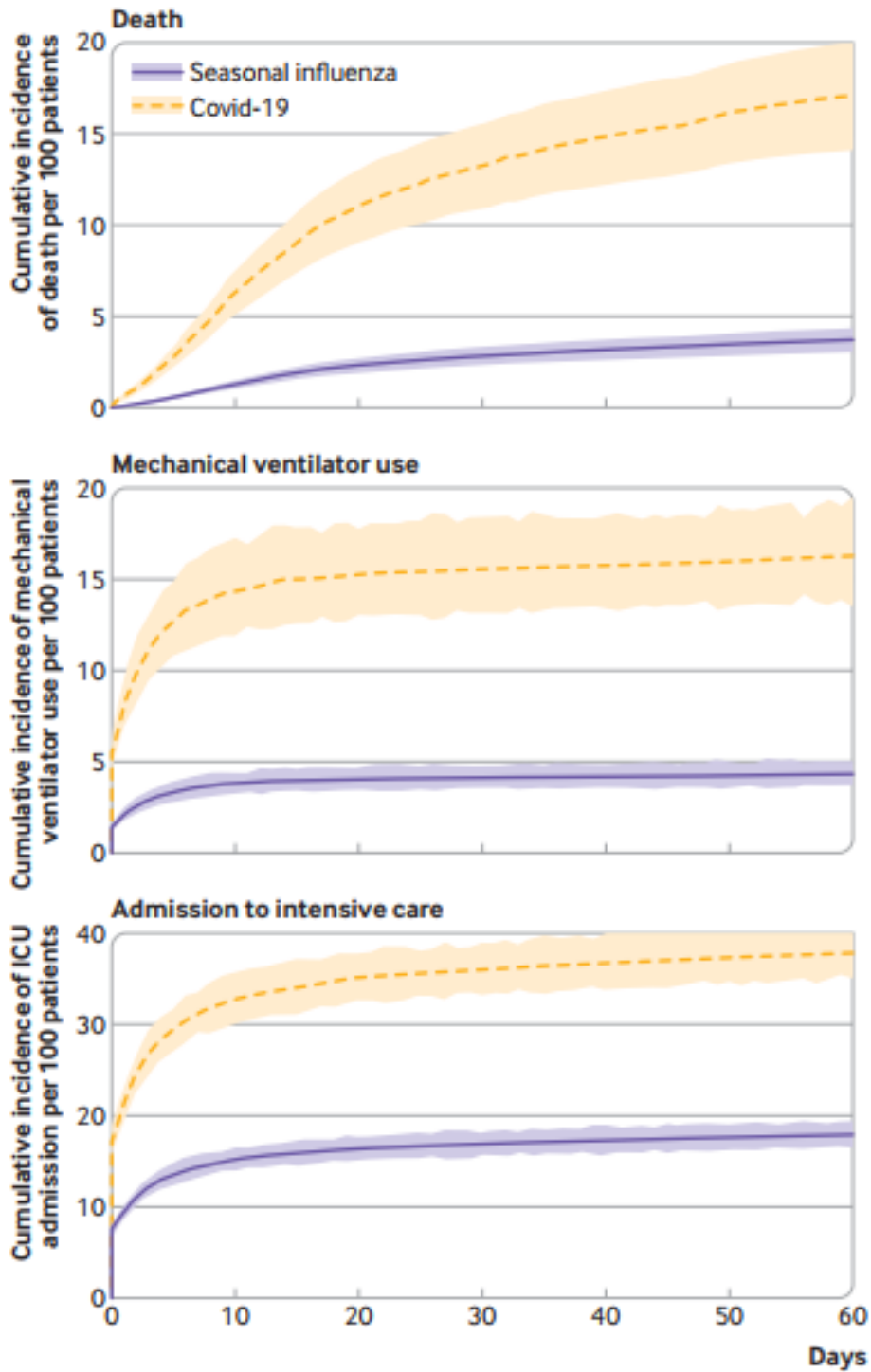
Comment: COVID-19 was also associated with increased health resource use, including mechanical ventilator use, admission to intensive care, and length of hospital stay, and nearly five times the risk of death. The differences in death rates between COVID-19 and seasonal influenza were most manifest in

older adults with kidney disease or dementia and black people with obesity, diabetes, or kidney disease. They did several sensitivity analyses to test the robustness of their results. First, because mortality from seasonal influenza may vary by season, they developed sensitivity analyses to examine the risk of death and health resource use in COVID-19 patients compared with those admitted with influenza in each season (2016-17, 2017-18, 2018- 19, 2019-20) separately; the results were consistent. Second, they looked at increased risk in COVID-19 versus seasonal influenza in analyses in which the reference group was those influenza patients who received an influenza vaccine and, separately, those who did not receive an influenza vaccine. The increased risk in COVID-19 versus seasonal influenza was observed in analyses in which the reference group was those influenza patients who received an influenza vaccine and, separately, those who did not receive an influenza vaccine. Third, because subtypes of influenza A may have differential effects on health outcomes and because the predominant subtype of influenza A may vary by season, they examined the association of COVID-19 versus influenza A in each season; the results suggested that compared with influenza A, COVID-19 was associated with increased risk of health resource use and death in each of the examined seasons. Fourth because our cohort comprised mostly male US veterans, and to examine whether the observed associations were also evident among female patients, they did analyses in subgroups based on sex; the results were consistent in both male and female subgroups. Finally, to test whether the observed associations were evident in smokers and non-smokers and, separately, among people with normal weight and obesity, they evaluated the association in subgroups according to smoking status and body mass index category; the results suggested that compared with seasonal influenza, COVID-19 was associated with increased risk of death and health resource use regardless of smoking and body mass index status. Their cohort comprised US veterans who were admitted to hospital for seasonal influenza or COVID-19 and included mostly older white males, so their results may not be generalizable to broader populations such as younger and healthier people. See above on current status of influenza and other respiratory viruses so far this season.

**Mobility Network Models of COVID-19 Explain Inequities and Inform Reopening**
Nature published online November 10,2020
https://doi.org/10.1038/s41586-020-2923-3
The investigator developed a metapopulation susceptible– exposed–infectious–removed (SEIR) model that integrates fine-grained, dynamic mobility networks to simulate the spread of SARS-CoV-2 in ten of the largest US metropolitan areas. Their mobility networks are derived from mobile phone data and map the hourly movements of 98 million people from neighborhoods (or census block groups) to points of interest such as restaurants and religious establishments, connecting 56,945 census block groups to 552,758 points of interest with 5.4 billion hourly edges. [impressive]

They showed that by integrating these networks, a relatively simple SEIR model can accurately fit the real case trajectory, despite substantial changes in the behavior of the population over time. Their model predicts that a small minority of 'superspreader' points of interest account for a large majority of the infections, and that restricting the maximum occupancy at each point of interest is more effective than uniformly reducing mobility. Their model also correctly predicts higher infection rates among disadvantaged racial and socioeconomic groups solely as the result of differences in mobility: they found that disadvantaged groups have not been able to reduce their mobility as sharply, and that the points of interest that they visit are more crowded and are therefore associated with higher risk. By capturing who is infected at which locations, our model supports detailed analyses that can inform more-effective and equitable policy responses to COVID-19.

Data revealed there's a "sweet spot" where infections can be reduced while keeping business steady. That magic number: around 20 percent. If indoor capacity in public spaces like restaurants, gyms, hotels and grocery stores was reduced to just 20 percent, they estimate this could prevent 87 percent of new infections. Meanwhile, these businesses would lose just 42 percent of their visits, on average. These findings bolster capacity limits as an effective coronavirus strategy, keeping businesses alive while limiting infections. Investigators found they are so effective because they reduce the risks during peak hours, encouraging patrons to stay home or visit at less crowded times. Rather than citywide shutdowns and stay-at-home orders, stricter density caps paired with other measures could curb SARS-CoV-2 while allowing the economy to stay open at a reduced rate. Occupancy limits alone will not prevent all transmissions. In places with greater underlying immunity and higher share of people wearing masks and social distancing, density caps are more likely to succeed. But they will not be as effective if the area's infections are rapidly worsening or other mechanisms like private gatherings are driving the spread. [unfortunately, private gatherings are a key driver to current spread]
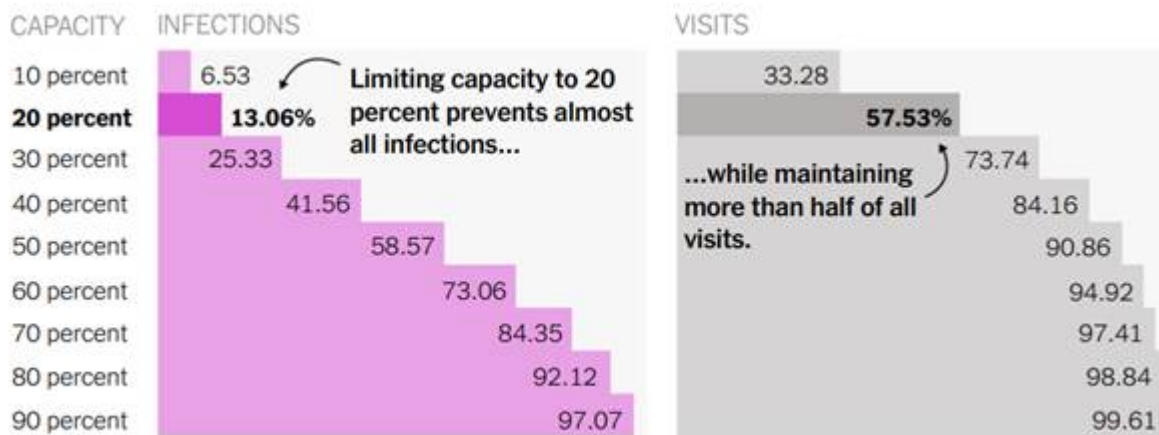
Comment: On average across metro areas, full-service restaurants, gyms, hotels, cafes, religious organizations, and limited-service restaurants produced the largest predicted increases in infections when reopened. These categories were predicted to have a higher risk because, in the mobility data, their POIs (points of interest) tended to have higher visit densities and/or visitors stayed there longer.

Global, Regional, and National Estimates of Target Population Sizes for COVID-19 Vaccination: Descriptive Study
doi.org/10.1136/bmj.m4704
Objective in this publication was to provide global, regional, and national estimates of target population sizes for COVID-19 vaccination to inform country specific immunization strategies on a global scale. (WHO 194 member states) Target populations for COVID-19 vaccination was based on country specific characteristics and vaccine objective (maintaining essential core societal services; reducing severe COVID-19; reducing symptomatic infections and stopping virus transmission). Estimates used country specific data on population sizes stratified by occupation, age, risk factors for COVID-19 severity, vaccine acceptance, and global vaccine production. These data were derived from a multipronged search of official websites, media sources, and academic journal articles.

Europe has the highest share of essential workers (63.0 million, 8.9%) and people with underlying conditions (265.9 million, 37.4%); these two categories are essential in maintaining societal

functions and reducing severe COVID-19, respectively. In contrast, South East Asia has the highest share of healthy adults (777.5 million, 58.9%), a key target for reducing community transmission. Vaccine hesitancy will probably impact future COVID-19 vaccination programs; based on a literature review, 68.4% (95% confidence interval 64.2% to 72.6%) of the global population is willing to receive COVID-19 vaccination. Therefore, the adult population willing to be vaccinated is estimated at 3.7 billion (95% confidence interval 3.2 to 4.1 billion).
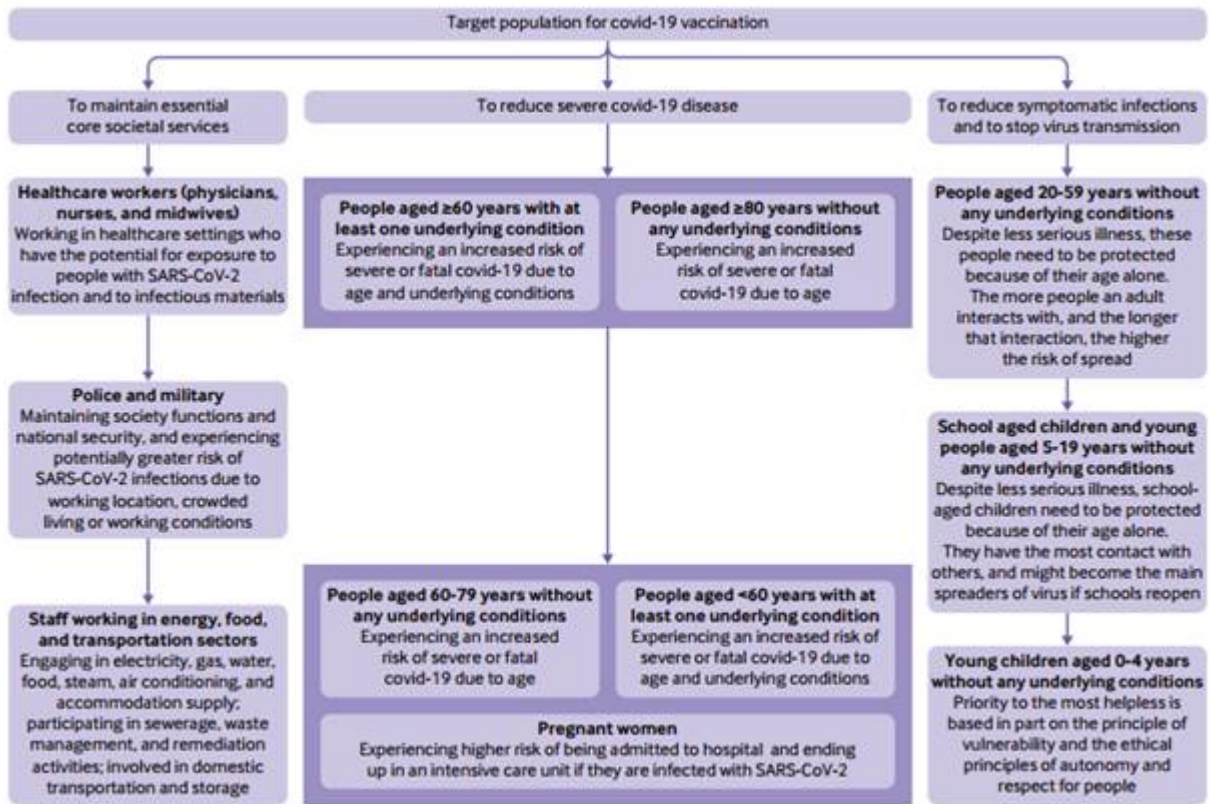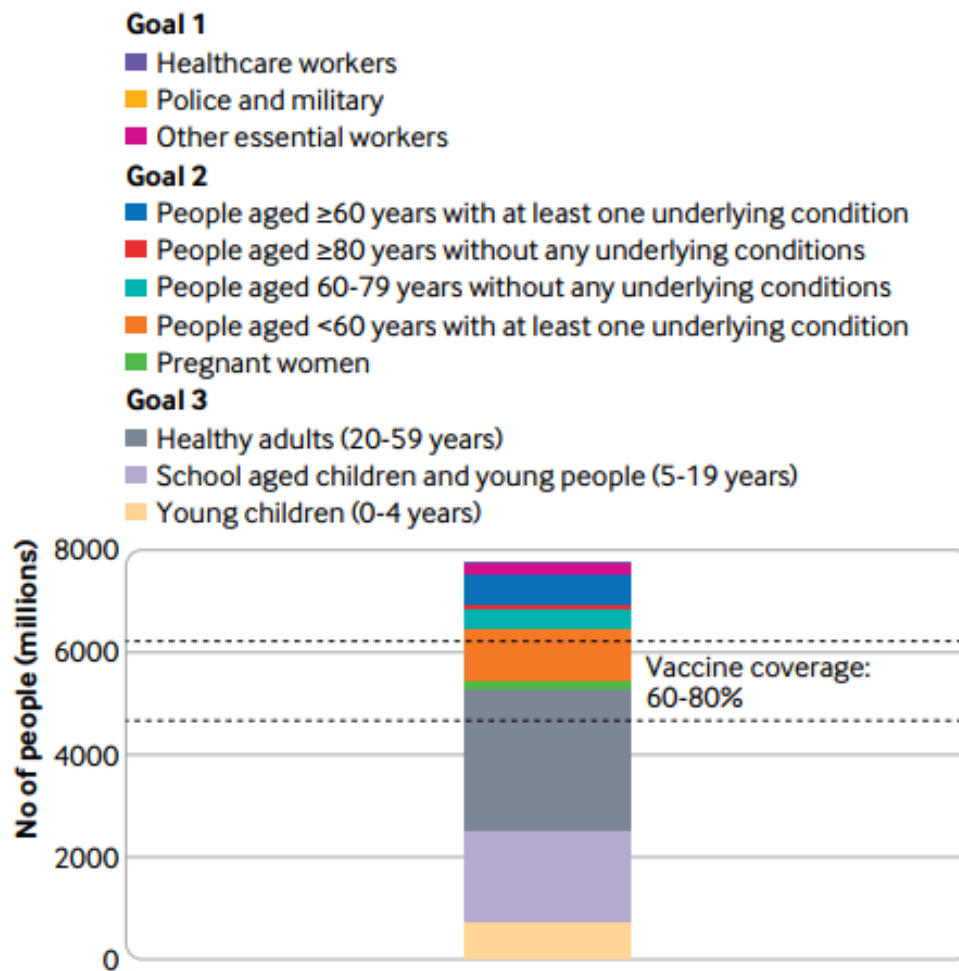

Fig 1 | Priority groups for covid-19 vaccination. Covid-19=coronavirus disease 2019; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2

Comment: Owing to geographical heterogeneity, regional and country specific allocation strategies should be designed to maintain functional societies, minimize COVID-19 burden, and reduce SARS-CoV-2 transmission. Vaccines that have three fundamental objectives: (1) To maintain essential core societal functions during the COVID-19 pandemic, such as essential health services and food delivery; (2) To protect people from irreversible and devastating harm, such as death and severe COVID-19 that causes long term organ damage (e.g., lung, kidney, CNS and liver); (3) To control community transmission, enabling a return to baseline prepandemic economic and social activities.

After HCW and LTC, the next vaccine allocation may target essential workers, which extends beyond HCW. Essential workers might include, but are not limited to, workers in the food industry and domestic transportation, police and military staff who maintain public safety, and workers who maintain electricity, water, fuel, information, and financial infrastructures. Teachers as essential workers are under discussion. The next vaccine allocation scheme targets people who might experience irreversible and devastating harm from COVID-19 (that is, admission to hospital, admission to critical care, and death). Target populations include people older than 65 years, those with high-risk health conditions,

and those in close contact with people at very high risk of poor outcomes. A next possible vaccine allocation scheme focuses on reducing SARS-CoV-2 transmission; in this case, high transmission groups should be targeted. Target populations include adults and children [current mRNA have not been studied in children <16 years of age] involved in economic or educational activities who experience higher risk of economic or educational harm from not working or going to school. These adults and children also have a higher probability of transmission when going back to work or school because of their large number of contacts. To reduce symptomatic infections and to stop virus transmission, vaccination should extend to all people younger than 60 years without any underlying conditions. These people can be vaccinated based on their risk of transmitting the virus, and projected economic harm from not working when considering the adult groups.

Goal 1
■ Healthcare workers
■ Police and military
■ Other essential workers
Goal 2
■ People aged ≥60 years with at least one underlying condition
■ People aged ≥80 years without any underlying conditions
■ People aged 60-79 years without any underlying conditions
■ People aged <60 years with at least one underlying condition
■ Pregnant women
Goal 3
■ Healthy adults (20-59 years)
■ School aged children and young people (5-19 years)
■ Young children (0-4 years)

Vaccine coverage: 60-80%

Fig 2 | Global estimates of target population sizes for covid-19 vaccination by goal of vaccination programmes. Covid-19=coronavirus disease 2019

Bottom line: Findings from this study provide an evidence base for global, regional, and national vaccine prioritization and allocation. Variations in the size of the target populations within and between regions emphasize the tenuous balance between vaccine demand and supply, especially in low- and middle-income countries without sufficient capacity to meet domestic demand for COVID-19 vaccine.

Regardless we must overcome vaccine hesitancy so we can reach herd immunity in the shortest period of time. Lastly, it is my opinion persons who have already had COVID-19 should go to the back of the line until we have enough vaccine to immunize everyone.

All-Cause Excess Mortality and COVID-19–Related Mortality Among US Adults Aged 25-44 Years, March-July 2020
JAMA published online December 16, 2020
doi:10.1001/jama2020.24243
To determine excess mortality (the gap between observed and expected deaths), projected monthly expected deaths for 2020 were calculated by applying autoregressive integrated moving averages to US population and mortality counts (2015-2019). They examined 2020 population and seasonal autoregressive integrated moving averages for each of the 10 HHS regions to determine excess mortality (the gap between observed and expected deaths), projected monthly expected deaths for 2020 were calculated by applying autoregressive integrated moving averages to US population and mortality counts (2015-2019). Incident rates per 100 000 person-months with 95% CIs were calculated for COVID-19.

From March 1, 2020, to July 31, 2020, a total of 76 088 all-cause deaths occurred among US adults aged 25 to 44 years, which was 11 899 more than the expected 64 189 deaths (incident rate ratio, 1.19 [95% CI, 1.14-1.23]. Among adults aged 25 to44years, 4535 COVID-19 deaths were recorded, accounting for 38% (95% CI, 32%-48%) of the measured excess mortality.

Comment: The COVID-19 pandemic was associated with increases in all-cause mortality among US adults aged 25 to 44 years from March through July of 2020. In 3 HHS regions, COVID-19 deaths were similar to or exceeded unintentional opioid overdoses that occurred during several corresponding months of 2018! What we believed before about the relative low risk of Covid-19 among younger adults has simply not been borne out by emerging data. We need to tell young people that they are at risk and that they need to wear masks and make safer choices about social distancing. Younger healthy adults are low on the priority list for the vaccine rollout. That means that modifying behavior now can save thousands of young lives next year.