RAOM COVID-19 ARCHIVE

January-March 2021

CONTENTS:

THE VIRUS

Washington NL, Karthik Gangavarapu K, Mark Zeller M et al. **Genomic epidemiology identifies emergence and rapid transmission of SARS-CoV-2 B.1.1.7 in the United States.** https://doi.org/10.1101/2021.02.06.21251159.

- As of January of 2021, the highly transmissible B.1.1.7 variant of SARS-CoV-2, first identified in the U.K., has gained a strong foothold across the world.
- We investigated the prevalence and growth dynamics of B.1.1.7 variant of SARS-CoV-2 in the U.S., tracking it back to its early emergence and onward local transmission.
- Using the RT-qPCR testing anomaly of S gene target failure (SGTF), first observed in the U.K. as a reliable proxy for B.1.1.7 detection, we sequenced 212 B.1.1.7 SARS-CoV-2 genomes collected from testing facilities in the U.S. from December 2020 to January 2021.
- While the fraction of B.1.1.7 among SGTF samples varied by state, detection of the variant increased at a logistic rate similar to those observed elsewhere, with a doubling rate of a little over a week and an increased transmission rate of 35-45%. enabling the variant to spread to at least 30 states as of January 2021.
- Our study shows that the U.S. is on a similar trajectory as other countries where B.1.1.7 rapidly became the dominant SARS-CoV-2 variant, requiring immediate and decisive action to minimize COVID-19 morbidity and mortality.

****

Hodcraft EB, Domman DB, Oguntuyo K et al. **Emergence in late 2020 of multiple lineages of SARS-CoV-2 Spike protein variants affecting amino acid position 677.** medRxiv 2021.02.12.21251658; **doi: https://doi.org/10.1101/2021.02.12.21251658**

- The SARS-CoV-2 spike protein (S) plays critical roles in host cell entry. Non-synonymous substitutions affecting S are not uncommon and have become fixed in a number of SARS-CoV-2 lineages. A subset of such mutations enable escape from neutralizing antibodies or are thought to enhance transmission through mechanisms such as increased affinity for the cell entry receptor, ACE2.
- Independent genomic surveillance programs based in New Mexico and Louisiana contemporaneously detected the rapid rise of numerous clade 20G (lineage B.1.2) infections

carrying a Q677P substitution in S. The variant was first detected in the US on October 23, yet between 01 Dec 2020 and 19 Jan 2021 it rose to represent 27.8% and 11.3% of all SARS-CoV-2 genomes sequenced from Louisiana and New Mexico, respectively.
- Q677P cases have been detected predominantly in the south central and southwest US; as of 03 Feb 2021, GISAID data show 499 viral sequences of this variant. Phylogenetic analyses revealed the independent evolution and spread of at least six distinct Q677H sub-lineages, with first collection dates ranging from mid August to late November, 2020.
- Although sampling bias and founder effects may have contributed to the rise of S:677 polymorphic variants, the proximity of this position to the polybasic cleavage site at the S1/S2 boundary are consistent with its potential functional relevance during cell entry, suggesting parallel evolution of a trait that may confer an advantage in spread or transmission.

****

Johansson MA, Quandelacy TM, Kada S, et al. **SARS-CoV-2 Transmission from People Without COVID-19 Symptoms.** JAMA Network Open. 2021;4(1):e2035057. Published 1/7/2021. **doi:10.1001/jamanetworkopen.2020.35057**

- To assess the proportion of SARS-CoV-2 transmissions in the community that likely occur from persons without symptoms, a decision analytic model was created to estimate the relative amount of transmission from presymptomatic, never symptomatic, and symptomatic individuals across a range of scenarios in which the proportion of transmission from people who never develop symptoms and the infectious period were varied according to published best estimates.
- The incubation period was set at a median of 5 days, the infectious period duration was maintained at 10 days, and peak infectiousness was varied between 3 and 7 days (−2 and +2 days relative to the median incubation period).
- The baseline assumptions for the model were that peak infectiousness occurred at the median of symptom onset and that 30% of individuals with infection never develop symptoms and are 75% as infectious as those who do develop symptoms.
- RESULTS: In this base case, 59% of all transmission came from asymptomatic transmission, 35% from presymptomatic individuals and 24% from individuals who never develop symptoms.
- Under a broad range of values for each of these assumptions, at least 50% of new SARS-CoV-2 infections was estimated to have originated from exposure to individuals with infection but without symptoms.
- → Effective control of SARS-CoV-2 spread will require reducing the risk of transmission from people with infection who do not have symptoms by social mitigation measures until safe and effective vaccines are widely used.

****

Beyer RM, Manica A, Mora C. **Shifts in global bat diversity suggest a possible role of climate change in the emergence of SARS-CoV-1 and SARS-CoV-2.** Science of The Total Environment, 2021. https://doi.org/10.1016/j.scitotenv.2021.145413.

- Bats have a special place amongst animal pathogen hosts in that they carry the highest proportion of zoonotic viruses of all mammalian orders. Coronaviruses (CoVs) account for over a third of the sequenced bat virome, corresponding to an estimated more than 3000

different CoVs carried by the world's bats. Several CoVs known to infect humans have very likely originated in bats including the 3 types associated with human fatalities: MERS CoV, SARS (CoV-1) and SARS-CoV-2.

- The number of CoVs present in an area is strongly correlated with local bat species richness, which in turn is affected by climatic conditions that drive the geographical distributions of species.
- Strains of CoV found in bats in the southern Chinese Yunnan province currently most closely resemble both SARS-CoV-1 and SARS CoV-2, suggesting this area is a plausible place of origin of the bat-borne ancestors of the two lineages. These regions also comprise the native habitat of masked palm civits and Sunda pangolins which are assumed to have acted as intermediate hosts that eventually transmitted SARS-CoV-1 and SARS-CoV-2 to humans.
- This study estimated species-specific geographical ranges of the world's bats based on global climatic conditions in the early 20th century and at present day, by first determining the global distribution of natural vegetation corresponding to a given climate, and then combining the derived vegetation maps with data on the spatial distribution and vegetation requirements of individual species.
- The global distribution of bats at each of the two time periods was then determined by combining the relevant vegetation map with species-specific data available for all known bats: extents of occurrence (the outermost geographic limits of a species' observed/projected occurrence) & habitat requirements.
- → In this way, the geographical range of each individual bat species was estimated for the early 20th century and for the present. Finally, the total bat species richness in each grid cell was obtained as the number of species whose estimated geographic range included the grid cell at the relevant time period.
- RESULTS: Areas estimated to have experienced significant increases in bat species richness as the result of climate change-driven range shifts include regions around Central Africa, several scattered patches in Central and South America, and notably a large spatial cluster located in the southern Chinese Yunnan province and neighboring regions in Myanmar and Laos.
- This region coincides with the likely spatial origin of bat-borne ancestors of SARS-CoV-1 and SARS-CoV-2. Accounting for an estimated increase in the order of 100 bat-borne CoVs across the region, climate change may have played a key role in the evolution or transmission of the two SARS CoVs.

****

Challen R, Brooks-Polek E, Read JM et al. **Risk of mortality in patients infected with SARS-CoV-2 variant of concern 202012/1: matched cohort study.** BMJ 2021; 372. (10 March 2021) **doi: https://doi.org/10.1136/bmj.n579**

- To establish whether there is any change in mortality from infection with the new UK variant of SARS-CoV-2, 54 906 matched pairs of participants who tested positive for SARS-CoV-2 between 1 October 2020 and 29 January 2021, were followed-up until 12 February 2021.
- Participants were matched on age, sex, ethnicity, multiple deprivation index, lower tier local authority region & sample date of (+) specimens, & differed only by detectability of the spike protein gene using the TaqPath assay, a proxy identifier for the UK variant of concern (VOC202012/1) aka B.1.1.7.

- Main outcome measure was death within 28 days of the first positive SARS-CoV-2 test result.
- RESULTS: The mortality hazard ratio associated with infection with B.1.1.7 compared with infection with previously circulating variants was 1.64 (95% confidence interval 1.32 to 2.04) in patients who tested positive for covid-19 in the community. In this comparatively low risk group, this represents an increase in deaths from 2.5 to 4.1 per 1000 detected cases.
- CONCLUSIONS: The probability that the risk of mortality is increased by infection with VOC-202012/01/B.1.1.7 is high. If this finding is generalizable to other populations, infection with VOC-202012/1 has the potential to cause substantial additional mortality compared with previously circulating variants.

Davies, N.G., Jarvis, C.I., CMMID COVID-19 Working Group. et al. **Increased mortality in community-tested cases of SARS-CoV-2 lineage B.1.1.7.** Nature 2021. https://doi.org/10.1038/s41586-021-03426-1

- By analyzing a dataset linking 2,245,263 positive SARS-CoV-2 community tests and 17,452 COVID-19 deaths in England from 1 September 2020 to 14 February 2021, these investigators assessed disease severity related to infection with the B.1.1.7 variant.
- For 1,146,534 (51%) of these tests, the presence or absence of B.1.1.7 can be identified because of mutations in this lineage preventing PCR amplification of the spike gene target, S gene target failure, SGTF1.
- RESULTS: Based on 4,945 deaths with known SGTF status, we estimate that the hazard of death associated with SGTF is 55% (95% CI 39–72%) higher after adjustment for age, sex, ethnicity, deprivation, care home residence, local authority of residence and test date.
- This corresponds to the absolute risk of death for a 55–69-year-old male increasing from 0.6% to 0.9% (95% CI 0.8–1.0%) within 28 days after a positive test in the community. Correcting for misclassification of SGTF and missingness in SGTF status, we estimate a 61% (42–82%) higher hazard of death associated with B.1.1.7.
- CONCLUSION: Our analysis suggests that B.1.1.7 is not only more transmissible than preexisting SARS-CoV-2 variants, but may also cause more severe illness.

****

Mendes Coutinho R, Marquitti FMD, Souto Ferreira L et al. **Model-based evaluation of transmissibility and reinfection for the P.1 variant of SARS-CoV-2.** medRxiv preprint, posted March 5, 2021. **https://doi.org/10.1101/2021.03.03.21252706.**

- The P.1 variant of SARS-VoV-2 emerged in the Amazonas state (Brazil) and was sequenced for the first time on 6-Jan-2021. It contains a constellation of mutations, ten in the spike protein. From December-2020 to February-2021, the Manaus province of Brazil was devastated by 4X more cases vs, the previous peak (April-2020). Prevalence of P.1 increased sharply from 0% in November 2020 to 73% in January 2021; in <2 mos, P.1 replaced previous lineages as the dominant pattern.
- In this study, data from the national health surveillance of hospitalized individuals were analyzed using a model-based approach to estimate P.1 transmissibility & reinfection parameters by maximum likelihood. Sensitivity analysis was performed changing pathogenicity & the analysis period.

- RESULTS: In all analyzed cases, the new variant transmissibility is found to be ~2.5 times higher compared to the previous variant in Manaus (CI: 2.1-2.8). The reinfection probability due to the new variant is 6.4% (95% CI: 5.7 - 7.1%). The model estimated that at the time the new variant emerged, the prevalence of the wild variant was 68% (95% CI: 63-74%).
- CONCLUSION: The consequences of the introduction of a highly transmissible variant have already been observed with the B.1.1.7 variant in the UK, USA and Europe. Higher transmissibility of the P.1 variant raises important concerns about more accelerated upsurges in the number of cases once P.1 spreads in the community in other parts of Brazil. Urgent mitigation measures are needed to control the spread of P.1.

THE DISEASE

Pandanaboyana S, Moir J, Leeds JS et al. **SARS-CoV-2 infection in acute pancreatitis increases disease severity and 30-day mortality: COVID PAN collaborative study.** Gut 2021. Epub ahead of print. Feb. 5, 2021. **http://dx.doi.org/10.1136/gutjnl-2020-323364.**

- Emerging evidence indicates that the pancreas may be a target organ of SARS-CoV-2 infection. To investigate the outcome of pts with acute pancreatitis (AP) and coexistent SARS-CoV-2 infection, a prospective international multicentre cohort study of consecutive pts admitted with AP during the current pandemic was undertaken.
- Primary outcome measure was severity of AP. Secondary outcome measures were aetiology of AP, intensive care unit (ICU) admission, length of hospital stay, local complications, acute respiratory distress syndrome (ARDS), persistent organ failure and 30-day mortality.
- 1777 pts with AP were included during the study period from 1 March to 23 July 2020. 149 pts (8.3%) had concomitant SARS-CoV-2 infection.
- RESULTS: Overall, SARS-CoV-2-positive pts were older, male and more likely to develop severe AP and ARDS (all, p<0.001). Unadjusted analysis showed that SARS-CoV-2-positive pts with AP were more likely to require ICU admission (OR 5.21, p<0.001), local complications (OR 2.91, p<0.001), persistent organ failure (OR 7.32, p<0.001), prolonged hospital stay (OR 1.89, p<0.001) and a higher 30-day mortality (OR 6.56, p<0.001).
- Adjusted analysis showed length of stay (OR 1.32, p<0.001), persistent organ failure (OR 2.77, p<0.003) and 30-day mortality (OR 2.41, p<0.04) were significantly higher in SARS-CoV-2 co-infection.
- CONCLUSION: Patients with AP and coexistent SARS-CoV-2 infection are at increased risk of severe AP, worse clinical outcomes, prolonged length of hospital stay and high 30-day mortality.

****

Villerabel C, Makinson A, Jaussent A, et al. **Diagnostic Value of Patient-Reported and Clinically Tested Olfactory Dysfunction in a Population Screened for COVID-19.** JAMA Otolaryngol Head Neck Surg. Published online January 07, 2021. **doi:10.1001/jamaoto.2020.5074**

- To prospectively evaluate the diagnostic value of a semiobjective olfactory test to assess patient-reported chemosensory dysfunction prior to testing for the presence of SARS-CoV-2, 809 consecutively screened pts were evaluated
- Pts were screened for symptoms and underwent Clinical Olfactory Dysfunction Assessment (CODA), via rapid evaluation of olfactory function using identification and rated intensity of lavender, lemongrass, and mint to achieve a summed score ranging from 0 to 6.
- COVID-19 status was assessed using reverse transcriptase–polymerase chain reaction to detect the presence of SARS-CoV-2 in samples collected via N-P swab.
- RESULTS: Of 809 participants, 58 (7.2%) tested positive for SARS-CoV-2. Chemosensory dysfunction was reported by 20 of 58 participants (34.5%) with confirmed COVID-19 vs 29 of 751 participants (3.9%) who tested negative for COVID-19 (absolute difference, 30.6% [95% CI, 18.3%-42.9%]).
- Olfactory dysfunction, either self-reported or clinically ascertained (CODA score ≤3), yielded similar sensitivity (0.31 [95% CI, 0.20-0.45] vs 0.34 [95% CI, 0.22-0.48]) and specificity (0.97

[95% CI, 0.96-0.98) vs 0.98 [95% CI, 0.96-0.99]) for COVID-19 diagnosis. The CODA score also revealed 5 of 19 participants (26.3%) with confirmed COVID-19 who had previously unperceived olfactory dysfunction.
- CONCLUSIONS: In this prospective diagnostic study of outpts with asymptomatic to moderate COVID-19, olfactory dysfunction was present in 34.5% and was strongly suggestive of COVID-19.

****

Nauen DW, Hooper JE, Stewart M, Solomon IH. **Assessing Brain Capillaries in Coronavirus Disease 2019**. JAMA Neurol. Published online February 12, 2021. **doi:10.1001/jamaneurol.2021.0225**

- Acutely ill COVID-19 pts often have confusion and alteration of consciousness and in recovery, many experience continued neurologic symptoms. However, in autopsies from COVID-19 pts, neurologic abnormalities have largely not identified the chronic inflammation or marked neural changes typically associated with viral infection, and viral genetic material has been minimal or absent.
- To evaluate this, brain tissue from 15 pts with COVID-19 & neurologic symptoms and 2 control pts in the same age group who died of hypoxia/ischemia underwent detailed histopathologic evaluation.
- RESULTS: In 5 cases in cortical capillaries, we identified large cell nuclei morphologically consistent with megakaryocytes. To further characterize these cells, we performed immunohistochemistry for CD61 and CD42b, markers of platelets and megakaryocytes. CD61 labels these cells, as does CD42b, confirming their megakaryocyte identity. The cells were distinct from platelet clusters, which were found in postmortem intravascular precipitates. Evaluation of the cortex of 2 patients who tested negative for COVID-19 who had hypoxic brain changes demonstrated no megakaryocytes on CD61.
- CONCLUSION/IMPLICATIONS: Multiple lines of evidence indicate endothelial dysfunction in severe COVID-19 illness. Lung examination demonstrates megakaryocytes and the cells have now been reported in other organs. One possibility is that altered endothelial or other signaling is recruiting megakaryocytes into the circulation and somehow permitting them to pass through the lungs. Megakaryocytes were found in cortical capillaries in 33% of cases examined. Because the standard brain autopsy sections taken sampled only a minute portion of the cortical volume, finding these cells suggests the total burden could be considerable. By occluding flow through individual capillaries, these large cells could cause ischemic alteration in a distinct pattern, potentially resulting in an atypical form of neurologic impairment.

****

Logue JK, Franko NM, McCulloch DJ, et al. **Sequelae in Adults at 6 Months After COVID-19 Infection**. JAMA Network Open. 2021;4(2):e210830. **doi:10.1001/jamanetworkopen.2021.0830.**

- A longitudinal prospective cohort of adults with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was enrolled at the University of Washington with a concurrent cohort of healthy patients in a control group. A total of 234

participants with COVID-19 were contacted to complete a single follow-up questionnaire between 3 and 9 months after illness onset between August and November 2020.

- A total of 177 of 234 participants (75.6%; mean [range] age, 48.0 [18-94] years; 101 [57.1%] women) with COVID-19 completed the survey. Overall, 11 (6.2%) had been asymptomatic, 150 (84.7%) were outpatients with mild illness, and 16 (9.0%) had moderate or severe disease requiring hospitalization. The follow-up survey was completed a median (range) of 169 (31-300) days after illness onset among participants with COVID-19.
- RESULTS: Among COVID-19 pts, persistent symptoms were reported by 17 of 64 (26.6%) aged 18 to 39 years, 25 of 83 (30.1%) aged 40 to 64 years, and 13 of 30 (43.3%) aged 65 years and older. Overall, 49 of 150 outpatients (32.7%), 5 of 16 hospitalized patients (31.3%), and 1 of 21 healthy participants (4.8%) in the control group reported at least 1 persistent symptom.
- The most common persistent symptoms were fatigue (24 of 177 patients [13.6%]) and loss of sense of smell or taste (24 patients [13.6%]). A total of 51 outpatients and hospitalized patients (30.7%) reported worse HRQoL compared with baseline vs 4 healthy participants and asymptomatic patients (12.5%); 14 patients (7.9%) reported negative impacts on at least 1 activity of daily living (ADL), the most common being household chores.
- CONCLUSION: In this cohort of individuals with COVID-19 who were followed up for as long as 9 months after illness, approximately 30% reported persistent symptoms.

****

Ayoubkhani D, Khunti K, Nafilyan V et al**. Post-COVID syndrome in individuals admitted to hospital with COVID-19: retrospective cohort study.** BMJ 2021; 372: n693. Published 31 March 2021. **doi: https://doi.org/10.1136/bmj.n693**

- To quantify rates of organ specific dysfunction in individuals with COVID-19 after hospital discharge, a retrospective cohort study was performed in 47,780 individuals(mean age 65, 55% men) after discharge from NHS hospitals compared with a matched control group from the general population.
- Main outcome measures: Rates of hospital readmission (or any admission for controls), all-cause mortality, diagnoses of respiratory, cardiovascular, metabolic, kidney, and liver diseases until 30 September 2020. Variations in rate ratios by age, sex, and ethnicity.
- RESULTS: Over a mean follow-up of 140 days, nearly a third of individuals who were discharged from hospital after acute COVID-19 were readmitted (14 060 of 47 780) and more than 1 in 10 (5875) died, with these events occurring at rates four and eight times greater than in the matched control group.
- Rates of respiratory disease (P<0.001), diabetes (P<0.001), and cardiovascular disease (P<0.001) were significantly raised in COVID-19 pts, with 770 (95% confidence interval 758 to 783), 127 (122 to 132), and 126 (121 to 131) diagnoses per 1000 person years, respectively.
- Rate ratios were greater for individuals aged less than 70 than for those aged 70 or older, and in ethnic minority groups compared with the white population, with the largest differences seen for respiratory disease (10.5 (95% confidence interval 9.7 to 11.4) for age less than 70 years v 4.6 (4.3 to 4.8) for age ≥70, and 11.4 (9.8 to 13.3) for non-white v 5.2 (5.0 to 5.5) for white individuals).
- CONCLUSION: Individuals discharged from hospital after COVID-19 had increased rates of multiorgan dysfunction compared with the expected risk in the general population. The

increase in risk was not confined to the elderly and was not uniform across ethnicities. The diagnosis, treatment, and prevention of post-covid syndrome requires integrated rather than organ or disease specific approaches, and urgent research is needed to establish the risk factors.

EPIDEMIOLOGY

Falk A, Benda A, Falk P, Steffen S, Wallace Z, Høeg TB. **COVID-19 Cases and Transmission in 17 K–12 Schools — Wood County, Wisconsin, August 31–November 29, 2020.** MMWR Morb Mortal Wkly Rep 2021;70:136–140. DOI: http://dx.doi.org/10.15585/mmwr.mm7004e3

- To assess in-school transmission of SARS-CoV-2, COVID-19 cases, spread, and compliance with mask use were investigated among 4,876 students and 654 staff members who participated in in-person learning in 17 K–12 schools in rural Wisconsin from August 31–November 29, 2020.
- Participating schools were from three public school districts, one private school district, and one independent private school. Eight schools were elementary (grades K–6) with 1,529 students attending in-person, and 9 were secondary (grades 7–12) with 3,347 students attending in-person.
- Basic COVID-19 precautions were in place: (1) Masking was required for all students and staff members at all schools. Students were asked to wear masks when within 6 feet of another person outdoors and at all times indoors. (2) Classroom cohorts of 10-12 students from one grade level were created with avoidance of mixing between cohorts. (3) Staff members were instructed to wear masks, maintain a distance of 6 feet from all persons and limit time in shared indoor spaces.
- COVID-19 cases in schools were reported by public health or school administration officials using deidentified data. Infection source was determined by case investigations conducted by school administration and the public health department.
- When a school was alerted to a positive case in a student or staff member, school officials identified persons who had had close contact and close contacts were required to quarantine in their homes. If they experienced symptoms during the quarantine period, they were further investigated to determine whether in-school spread might have occurred.
- RESULTS: 4,876 students and 654 staff members contributed data to the study. During the 13-week study period, a total of 3,393 COVID cases were reported in Wood County (cumulative incidence = 5,466 per 100,000 persons), including 191 cases within the participating schools (cumulative incidence = 3,454 per 100,000).
- Cases occurred in 133 students and 58 staff members. Among these 191 cases, seven (3.7%) were attributed to in-school SARS-CoV-2 transmission, all among students. Five cases of transmission occurred in elementary school cohorts, and two in secondary school cohorts. Three of these seven cases occurred in one class in one elementary school, and the other four occurred at separate schools. No in-school transmission between separate classroom cohorts was reported.
- Weekly COVID-19 incidence ranged from 34 to 1,189/100,000 persons in the community, and from 72 to 699 cases/100,000 among students and staff in the schools. COVID-19 incidence in schools conducting in-person instruction was 37% lower than that in the surrounding community.
- Observed student masking compliance ranged from 92.1% to 97.4% and did not vary by student age.

****

Flannery DD, Gouma S, Dhudasia MB et al. **Assessment of Maternal and Neonatal Cord Blood SARS-CoV-2 Antibodies and Placental Transfer Ratios.** JAMA Pediatr. Published online January 29, 2021. **doi:10.1001/jamapediatrics.2021.0038.**

- To assess maternal and neonatal SARS-CoV-2–specific antibody concentrations, maternal and cord blood sera were assessed for antibodies in 1471 mother/newborn dyads. IgG and IgM antibodies to the receptor-binding domain of the SARS-CoV-2 spike protein were measured by enzyme-linked immunosorbent assay.
- Among the 1471 mother/newborn pairs for whom matched sera were available, SARS-CoV-2 IgG and IgM antibodies were detected in 6% of the women (83/1471) at the time of delivery, and IgG was detected in the cord blood of 87% of their newborns (72/83). IgM antibodies were not detected in any cord blood samples.
- Antibody transfer ratios were not associated with the severity of maternal SARS-CoV-2 infection but were associated with the time between maternal infection and delivery.
- These findings of transplacental transfer of SARS-CoV-2 antibodies indicate the potential of the antibodies to confer protection to the newborn from infection with COVID-19.

Wang QQ, Davis PB, Gurney ME, Xu R. **COVID-19 and dementia: Analyses of risk, disparity, and outcomes from electronic health records in the US.** Alzheimer's & Dementia 2021. First published: 09/02/2021. https://doi.org/10.1002/alz.12296

- To assess risk for COVID-19 in pts with dementia, a retrospective case-control analysis of EHRs of 61.9 million adult and senior pts (≥ 18 years) in the United States up to August 21, 2020 was conducted.
- RESULTS: Pts with dementia were at increased risk for COVID-19 compared to pts without dementia (adjusted odds ratio [AOR]: 2.00 (CI), 1.94–2.06], P < .001).
- The effect was strongest for vascular dementia (AOR: 3.17 [CI, 2.97–3.37], P < .001), followed by presenile dementia (AOR: 2.62 [CI, 2.28–3.00], P < .001), Alzheimer's disease (AOR: 1.86 [CI, 1.77–1.96], P < .001), senile dementia (AOR: 1.99 [CI, 1.86–2.13], P < .001) and post-traumatic dementia (AOR: 1.67 [CI, 1.51–1.86] P < .001).
- Blacks with dementia had higher risk of COVID-19 than Whites (AOR: 2.86 [CI, 2.67–3.06], P < .001).
- The 6-month mortality and hospitalization risks in pts with dementia and COVID-19 were 20.99% and 59.26%, respectively.

****

Tönshoff B, Muller B, Elling R et al. **Prevalence of SARS-CoV-2 Infection in Children and Their Parents in Southwest Germany.** JAMA Pediatr 2021; Jan 22, 2021.e210001. **doi: 10.1001/jamapediatrics.2021.0001.**

- To describe the rate of SARS-CoV-2 infections and the seroprevalence of SARS-CoV-2 antibodies in children aged 1 to 10 years, compared with a corresponding parent of each child, this large-scale, multicenter, cross-sectional investigation enrolled children aged 1 to 10 years and a corresponding parent between 4/22 & 5/15/2020, in southwest Germany.

- Participants were tested for SARS-CoV-2 RNA from nasopharyngeal swabs by reverse transcription–polymerase chain reaction and SARS-CoV-2 specific IgG antibodies in serum by enzyme-linked immunosorbent assays and immunofluorescence tests.
- RESULTS: This study included 4964 participants: 2482 children (median age, 6 [range, 1-10] years; 1265 boys [51.0%]) and 2482 parents (median age, 40 [range, 23-66] years; 615 men [24.8%]). The estimated SARS-CoV-2 seroprevalence was low in parents (1.8% [95% CI, 1.2–2.4%]) and 3-fold lower in children (0.6% [95% CI, 0.3-1.0%]). Among 56 families with at least 1 child or parent with seropositivity, the combination of a parent with seropositivity and a corresponding child with seronegativity was 4.3 (95% CI, 1.19-15.52) times higher than the combination of a parent who was seronegative and a corresponding child with seropositivity. We observed virus-neutralizing activity for 66 of 70 IgG-positive serum samples (94.3%).
- CONCLUSIONS: In this cross-sectional study, the spread of SARS-CoV-2 infection during a period of lockdown in southwest Germany was particularly low in children aged 1 to 10 years. Accordingly, it is unlikely that children have boosted the pandemic.

****

Williamson, E.J., Walker, A.J., Bhaskaran, K. et al. **Factors associated with COVID-19-related death using OpenSAFELY.** Nature 584, 430–436 (2020). https://doi.org/10.1038/s41586-020-2521-4

- OpenSAFELY—a secure health analytics platform that covers 40% of all pts in England and holds patient data in electronic health records – was used to examine factors associated with COVID-19-related death. From 17,278,392 adults, 10,926 COVID-19-related deaths were identified.
- RESULTS: Increasing age was strongly associated with risk, with people aged 80 or over having a **>20-fold-increased risk compared to 50–59-year-olds** (fully adjusted HR 20.60; 95% confidence interval (CI) With age fitted as a flexible spline, an approximately log-linear relationship was observed.
- People from all Black, Asian & mixed ethnic groups were at higher risk than those of white ethnicity. When adjusted only for age and sex, hazard ratios ranged from 1.62–1.88 for Blacks, South Asians & people of mixed ethnicities, decreasing to 1.43–1.48 after adjustment for all included factors.
- Increasing risks were seen with increasing obesity (adjusted HR 1.92 [1.72–2.13] for a BMI> 40kg/m2.
- Comorbidities associated with a higher risk of COVID-19-related death included DM, severe asthma (defined as asthma with recent use of an oral corticosteroid), respiratory disease, chronic heart disease, liver disease, stroke, dementia, reduced kidney function and autoimmune diseases.
- Those with a history of hematological malignancy in the last 5 yrs had a >2.5-fold increased risk, which decreased slightly after five years.
- CONCLUSIONS: In this very large study, previously identified risk factors for death from COVID-19 were confirmed and amplified. The most striking finding was the profound impact of increasing age.

****

Nguyen NT, Chinn J, Nahmias J et al. **Outcomes and Mortality Among Adults Hospitalized With COVID-19 at US Medical Centers.** JAMA Network Open. 2021;4(3):e210417. Published March 5,2021. **doi:10.1001/jamanetworkopen.2021.0417**

- To examine outcomes among adults hospitalized with COVID-19 at US medical centers and analyze changes in mortality over the initial 6-month period of the pandemic, data were obtained from the Vizient clinical database, an administrative, clinical, and financial database of more than 650 academic centers and their affiliates from 47 US states.
- Primary outcome was in-hospital mortality, analyzed according to the month of admission and age group, and in a subgroup of pts requiring intensive care unit (ICU) admission. Secondary outcomes included length of hospital stay, length of ICU stay, and median cost of ICU stay vs non-ICU stay.
- Among 192 550 adults hospitalized with COVID-19, 101 089 (52.5%) were men, 83 567 (43.3%) were White, and 125 543 (65.2%) had Medicare or Medicaid insurance. The most common comorbidities included hypertension (118 418 [61.5%]), diabetes (73 939 [38.4%]), and obesity (52 759 [27.4%]).
- RESULTS: 55 593 of pts (28.9%) were admitted to the ICU, 26 221 (13.6%) died during the index hospitalization, and 5839 (3.0%) were transferred to hospice care.
- In-hospital mortality increased with increasing age: 179 of 12 644 pts (1.4%) aged 18 to 29 years died vs. 8277 of 31 135 patients (26.6%) 80 years or older. Of pts admitted to the ICU, 15 431 of 55 593 (27.8%) died.
- There was a significant reduction in mortality over the course of the 6-month period, with the highest mortality in March (3657 of 16 517 patients died [22.1%]); mortality decreased each month until the end of the study period in August (1154 of 17 776 patients died [6.5%]) ($\chi 2$ for trend, 3592.3; $P < .001$)

****

Hattoriab T, Amishimaa M, Morinaga D et al. **Older age is associated with sustained detection of SARS-CoV-2 in nasopharyngeal swab samples.** Journal of Infection 2021; 82:159-198. **doi: 10.1016/j.jinf.2020.06.046.**

- Records of 66 pts diagnosed with COVID-19 between 3/1 & 4/30/2020 at National Hospital Organization, Hokkaido Medical Center were analyzed. PCR tests were performed daily on N/P samples.
- 42 subjects were mild cases, who did not require supplemental oxygen treatment. 18 subjects were moderate cases who needed oxygen treatment. 6 subjects were severe cases who needed ventilator or/and ECMO.
- RESULTS: Older age was significantly associated with prolonged positive PCR tests ($P = 0.0053$). This relationship remained unchanged when the findings were adjusted for the potential impact of severity of the disease and the use of medication ($P = 0.026$). When we analyzed only mild cases of COVID-19, the result remained significant ($P = 0.036$).
- In summary, old age is significantly associated with prolonged duration of positive PCR results from nasopharyngeal swab samples, regardless of disease severity. Further studies will be needed in order to clarify how long these patients are actually contagious.

TREATMENT

Schoof M, Faust B, Reuben A. Saunders RA et al. **An ultra-potent synthetic nanobody neutralizes SARS-CoV-2 by locking Spike into an inactive conformation**. BioRxiv 8/2020.
https://doi.org/10.1101/2020.08.08.238469.

- SARS-CoV-2 gains entry into host cells via interaction between its Spike protein and the host cell receptor angiotensin converting enzyme 2 (ACE2). → Disruption of this interaction confers potent neutralization of viral entry.
- By screening a yeast surface-displayed library of synthetic nanobody sequences, we identified a panel of nanobodies that bind to multiple epitopes on Spike & block ACE2 interaction via 2 distinct mechanisms.
- Cryogenic electron microscopy (cryo-EM) revealed that one exceptionally stable nanobody, Nb6, binds Spike in a fully inactive conformation with its receptor binding domains (RBDs) locked into their inaccessible down-state, incapable of binding ACE2.
- Affinity maturation & structure-guided multivalency design yielded a trivalent nanobody, mNb6-tri, with femtomolar affinity for SARS-CoV-2 Spike & picomolar neutralization of SARS-CoV-2 infection.
- mNb6-tri retains stability and function after aerosolization, lyophilization, and heat treatment. These properties may enable aerosol-mediated nasal spray delivery of this potent neutralizer directly to the airway epithelia, promising a widely deployable, patient-friendly prophylactic and/or early infection therapeutic agent to stem the worst pandemic in a century.

****

Gottlieb RL, Nirula A, Chen P et al. **Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19: A Randomized Clinical Trial**. JAMA. Published online January 21, 2021. **doi:10.1001/jama.2021.0202.**

- To determine the effect of antispike neutralizing antibodies, bamlanivimab monotherapy and combination therapy with bamlanivimab and etesevimab were compared in outpts with mild to moderate COVID-19.
- Ambulatory pts who tested positive for SARS-CoV-2 infection and had 1 or more mild to moderate symptoms were first randomized to receive bamlanivimab monotherapy or placebo from 6/17-8/21/2020, followed by bamlanivimab and etesevimab or placebo (8/22-9/3).
- The primary end point was change in SARS-CoV-2 log viral load at day 11 (±4 days). Nine prespecified secondary outcome measures were evaluated including the proportion of patients with a COVID-19–related hospitalization, an emergency department [ED] visit, or death at day 29.
- Results: Among the 577 patients who were randomized and received an infusion, the mean decrease in log viral load from baseline at day 11 was significantly greater for highest dose combination treatment vs placebo.

- Among the secondary outcome measures, the proportion of patients with COVID-19–related hospitalizations or ED visits was significantly lower for combination treatment.
- Conclusion: Among nonhospitalized patients with mild to moderate COVID-19 illness, treatment with bamlanivimab and etesevimab, compared with placebo, was associated with a statistically significant reduction in SARS-CoV-2 viral load at day 11; no significant difference in viral load reduction was observed for bamlanivimab monotherapy.

****

Horby PW, Campbell M, Staplin N et al. **Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial**. medRxiv – posted 2/11/2021. **doi: https://doi.org/10.1101/2021.02.11.21249258.**

- Between 4/23/2020 & 1/25/2021, 4116 adults were included in the assessment of tocilizumab, including 562 (14%) patients receiving invasive mechanical ventilation, 1686 (41%) receiving non-invasive respiratory support, and. 1868 (45%) receiving no respiratory support other than oxygen. 3385 (82%) patients were receiving systemic corticosteroids at randomisation.
- RESULTS: Overall, 596 (29%) of 2022 pts allocated to tocilizumab and 694 (33%) of 2094 pts allocated to usual care died within 28 days (rate ratio 0.86; 95% confidence interval [CI] 0.77-0.96; p=0.007).
- Consistent results were seen in all pre-specified subgroups of pts, including those receiving systemic corticosteroids: Pts allocated to tocilizumab were more likely to be discharged from hospital alive within 28 days (54% vs. 47%; rate ratio 1.23; 95% CI 1.12-1.34; p<0.0001); among those not receiving invasive mechanical ventilation at baseline, pts allocated tocilizumab were less likely to reach the composite endpoint of invasive mechanical ventilation or death (33% vs. 38%; risk ratio 0.85; 95% CI 0.78-0.93; p=0.0005).
- INTERPRETATION: In hospitalized COVID-19 patients with hypoxia and systemic inflammation, tocilizumab improved survival and other clinical outcomes regardless of the level of respiratory support received and in addition to the use of systemic corticosteroids.

****

Thomas S, Patel D, Bittel B, et al. **Effect of High-Dose Zinc and Ascorbic Acid Supplementation vs Usual Care on Symptom Length and Reduction Among Ambulatory Patients With SARS-CoV-2 Infection: The COVID A to Z Randomized Clinical Trial**. JAMA Netw Open. 2021;4(2):e210369. **doi:10.1001/jamanetworkopen.2021.0369**

- To examine whether high-dose zinc and/or high-dose ascorbic acid reduce the severity or duration of symptoms compared with usual care among ambulatory pts with SARS-CoV-2 infection, a multicenter, single health system RCT enrolled 214 adult pts with a PCR-confirmed diagnosis of SARS-CoV-2 infection who received outpt care in sites in Ohio and Florida between 4/27 and 10/14/2020.
- Pts were randomized in a 1:1:1:1 allocation ratio to receive either 10 days of zinc gluconate (50 mg), ascorbic acid (8000 mg), both agents, or standard of care.
- The primary end point was the number of days required to reach a 50% reduction in symptoms, including severity of fever, cough, shortness of breath, and fatigue (rated on a 4-point scale for each symptom). Secondary end points included days required to reach a total

symptom severity score of 0, cumulative severity score at day 5, hospitalizations, deaths, adjunctive prescribed medications, and adverse effects of the study supplements.

- RESULTS: A total of 214 pts were randomized, with a mean (SD) age of 45.2 (14.6) years and 132 (61.7%) women. The study was stopped for a low conditional power for benefit with no significant difference among the 4 groups for the primary end point. Pts who received usual care without supplementation achieved a 50% reduction in symptoms at a mean (SD) of 6.7 (4.4) days compared with 5.5 (3.7) days for the ascorbic acid group, 5.9 (4.9) days for the zinc gluconate group, and 5.5 (3.4) days for the group receiving both (overall P = .45). There was no significant difference in secondary outcomes among the treatment groups.
- CONCLUSIONS: In this randomized clinical trial of ambulatory pts diagnosed with SARS-CoV-2 infection, treatment with high-dose zinc gluconate, ascorbic acid, or a combination of the 2 supplements did not significantly decrease the duration of symptoms compared with standard of care.

****

Rentsch CT, Beckham JA, Tomlinson L et al. **Early initiation of prophylactic anticoagulation for prevention of coronavirus disease 2019 mortality in patients admitted to hospital in the United States: cohort study.** BMJ 2021; 372:n311. (Published 11 February 2021) **doi: https://doi.org/10.1136/bmj.n311**

- To evaluate whether early initiation of prophylactic anticoagulation compared with no anticoagulation was associated with decreased risk of death among pts admitted to hospital with COVID-19 in the US, all 4297 pts admitted to VA hospitals from 1 March to 31 July 2020 with laboratory confirmed SARS-CoV-2 infection and without a history of anticoagulation were enrolled.
- The main outcome was 30 day mortality. Secondary outcomes were inpatient mortality, initiating therapeutic anticoagulation (a proxy for clinical deterioration, including thromboembolic events), and bleeding that required transfusion.
- RESULTS: Of 4297 patients admitted to hospital with COVID-19, 3627 (84.4%) received prophylactic anticoagulation within 24 hours of admission. More than 99% (n=3600) of treated patients received subcutaneous heparin or enoxaparin. 622 deaths occurred within 30 days of hospital admission, 513 among those who received prophylactic anticoagulation. Most deaths (510/622, 82%) occurred during hospital stay.
- Using inverse probability of treatment weighted analyses, the cumulative incidence of mortality at 30 days was 14.3% (95% confidence interval 13.1% to 15.5%) among those who received prophylactic anticoagulation and 18.7% (15.1% to 22.9%) among those who did not. Compared with pts who did not receive prophylactic anticoagulation, those who did had a 27% decreased risk for 30 day mortality (hazard ratio 0.73, 95% confidence interval 0.66 to 0.81). Similar associations were found for inpatient mortality and initiation of therapeutic anticoagulation.
- Receipt of prophylactic anticoagulation was not associated with increased risk of bleeding that required transfusion (hazard ratio 0.87, 0.71 to 1.05).
- CONCLUSIONS: Early initiation of prophylactic anticoagulation compared with no anticoagulation among pts admitted to hospital with COVID-19 was associated with a decreased risk of 30 day mortality and no increased risk of serious bleeding events. These findings provide strong real-world evidence to support the use of prophylactic anticoagulation as initial treatment for pts with COVID-19 on hospital admission.

****

Murai IH, Fernandes AL, Sales LP et al. **Effect of a Single High Dose of Vitamin D3 on Hospital Length of Stay in Patients with Moderate to Severe COVID-19: A Randomized Clinical Trial.** JAMA. Published online February 17, 2021. **doi:10.1001/jama.2020.26848**.

- To investigate the effect of a single 200,000 IU dose of vitamin D3 on hospital length of stay in 420 hospitalized pts with COVID-19, a multicenter, double-blind, randomized, placebo-controlled trial was conducted in 2 sites from 6/2-8/27/2020.
- The primary outcome was length of stay = time from randomization to hospital discharge. Prespecified secondary outcomes included mortality during hospitalization; ICU admissions; # of pts who required mechanical ventilation/ duration of mechanical ventilation; and serum levels of 25-hydroxyvitamin D, total calcium, creatinine, and C-reactive protein.
- RESULTS: Of 237 includeded pts, median length of stay was not significantly different between the vitamin D3 (7.0 [4.0-10.0] days) and placebo groups (7.0 [5.0-13.0] days) (log-rank P = .59; unadjusted hazard ratio for hospital discharge, 1.07 [95% CI, 0.82-1.39]; P = .62).
- There were no significant differences between the vitamin D3 group & placebo groups for any secondary outcome.
- CONCLUSIONS: Among hospitalized pts with COVID-19, a single high dose of vitamin D3, compared with placebo, did not significantly reduce hospital length of stay.

****

López-Medina E, López P, Hurtado IC, et al. **Effect of Ivermectin on Time to Resolution of Symptoms Among Adults with Mild COVID-19: A Randomized Clinical Trial.** JAMA. Published March 04, 2021. **doi:10.1001/jama.2021.3071**

- To determine whether the anti-parasitic drug ivermectin is an efficacious treatment for mild COVID-19, a double-blind, RCT was conducted at a single site in Cali, Colombia.
- A total of 476 adult pts with mild disease and symptoms for 7 days or fewer (at home or hospitalized) were enrolled between 7/15 and 11/30, 2020, and followed up through December 21, 2020.
- Pts were randomized to receive ivermectin, 300 μg/kg/day for 5 days (n = 200) or placebo (n = 200).
- Primary outcome was time to resolution of symptoms within a 21-day follow-up period. Solicited adverse events and serious adverse events were also collected.
- RESULTS: Among 400 randomized pts who were randomized in the primary analysis, 398 (99.5%) completed the trial. Median time to resolution of symptoms was 10 days (IQR, 9-13) in the ivermectin group compared with 12 days (IQR, 9-13) in the placebo group (hazard ratio for resolution of symptoms, 1.07 [95% CI, 0.87 to 1.32]; P = .53 by log-rank test). By day 21, 82% in the ivermectin group and 79% in the placebo group had resolved symptoms.
- The most common solicited adverse event was headache, reported by 104 patients (52%) given ivermectin and 111 (56%) who received placebo. The most common serious adverse event was multiorgan failure, occurring in 4 patients (2 in each group).
- CONCLUSION: Among adults with mild COVID-19, a 5-day course of ivermectin, compared with placebo, did not significantly improve the time to resolution of symptoms.

****

Intravenous Aviptadil for Critical COVID-19 With Respiratory Failure (COVID-AIV). Reported by manufacturer, NeuroRx. Peer-reviewed publication pending.

- Aviptadil (Zyesami), an investigational formulation of vasoactive intestinal peptide delivered by IV infusion was evaluated in a 196-patient randomized trial.
- Primary endpoint of the phase IIb/III trial was defined as recovery from respiratory failure without relapse & discharge from acute care plus survival through a 60 day observation period.
- In a subgroup of 127 pts receiving high-flow nasal cannula support (n=127), those treated with aviptadil acetate had a 71% chance of successful recovery by day 28 compared with 48% of those receiving placebo (P=0.017); this increased to a 75% chance of recovery by day 60 versus 55% in the placebo group (P=0.036).
- 84% of patients in this high flow nasal cannula group receiving the intervention treated at tertiary medical centers survived to day 60 versus 60% of the placebo group (P=0.007).
- Aviptadil is the first COVID-19 therapeutic to demonstrate advantages in both survival and recovery from critical COVID-19 in a randomized, double-blind multicenter trial.

****

Chow JH, Khanna AK, Tethireddy S et al. **Aspirin Use Is Associated with Decreased Mechanical Ventilation, Intensive Care Unit Admission, and In-Hospital Mortality in Hospitalized Patients with Coronavirus Disease 2019.** Anesthesia & Analgesia: April 2021 - Volume 132 - Issue 4 - p 930-941 **doi: 10.1213/ANE.0000000000005292**

- To evaluate COVID-19 SEQUELAE, COVID-19 patients admitted to the hospital between March 2020 and July 2020 were abstracted from the multicenter collaborative research DATABASE.
- Four hundred twelve patients were included in the study. Median age was 55 years (IQR, 41–66 yrs), & 59.2% of patients were male. 98 pts (23.7%) received aspirin, while 314 pts (76.3%) did not.
- On unadjusted analysis, patients receiving aspirin had significantly lower rates of mechanical ventilation (35.7% [35/98] aspirin versus 48.4% [152/314] nonaspirin, P = .03) and ICU admission (38.8% [38/98] aspirin versus 51.0% [160/314] nonaspirin, P = .04).
- There was no crude difference in in-hospital mortality (26.5% [26/98] aspirin versus 23.2% [73/314] nonaspirin, P = .51) between groups.
- In addition, there was no difference in the rate of major bleeding (6.1% aspirin [6/98] versus 7.6% nonaspirin [24/314], P = .61), or overt thrombosis (8.2% [8/98] aspirin versus 8.9% [28/314] nonaspirin, P = .82) between groups.
- In this retrospective observational study, aspirin use was associated with a significantly lower rate of mechanical ventilation, intensive care unit (ICU) admission, and in-hospital mortality after controlling for confounding variables.
- CONCLUSIONS: Aspirin may have lung-protective effects and reduce the need for mechanical ventilation, ICU admission, and in-hospital mortality in hospitalized COVID-19 patients.

****

Grieco DL, Menga LS, Cesarano M et al. **Effect of Helmet Noninvasive Ventilation vs High-Flow Nasal Oxygen on Days Free of Respiratory Support in Patients With COVID-19 and**

Moderate to Severe Hypoxemic Respiratory Failure: The HENIVOT Randomized Clinical Trial. JAMA. Published online March 25, 2021. **doi:10.1001/jama.2021.4682**

- To assess whether helmet noninvasive ventilation can increase days free of respiratory support in 109 COVID-19 pts with moderate to severe hypoxemic respiratory failure, compared with high-flow nasal oxygen alone, a multi-center RCT was performed in 4 ICUs in Italy between 10 & 12/2020 with end of F/U, 2/11/2021.
- Pts were randomly assigned to receive continuous treatment with helmet noninvasive ventilation (positive end-expiratory pressure, 10-12 cm H2O; pressure support, 10-12 cm H2O) for at least 48 hours eventually followed by high-flow nasal O2 (n = 54) or high-flow O2 alone (60 L/min) (n = 55).
- Primary outcome was the number of days free of respiratory support within 28 days after enrollment. Secondary outcomes included the proportion of patients who required endotracheal intubation within 28 days from study enrollment, the number of days free of invasive mechanical ventilation at day 28, the number of days free of invasive mechanical ventilation at day 60, in-ICU mortality, in-hospital mortality, 28-day mortality, 60-day mortality, ICU & hospital length of stay.
- RESULTS: 109 pts (99%) completed the trial (median age, 65 years [interquartile range {IQR}, 55-70]; 21 women [19%]). Median days free of respiratory support within 28 days after randomization were 20 (IQR, 0-25) in the helmet group & 18 (IQR, 0-22) in the high-flow nasal O2 group, a difference that was not statistically significant (mean difference, 2 days [95% CI, −2 to 6]; P = .26). The rate of endotracheal intubation was significantly lower in the helmet group than in the high-flow nasal O2 group (30% vs 51%; difference, −21% [95% CI, −38% to −3%]; P = .03). The median number of days free of invasive mechanical ventilation within 28 days was significantly higher in the helmet group than in the high-flow nasal O2 group (28 [IQR, 13-28] vs 25 [IQR 4-28]; mean difference, 3 days [95% CI, 0-7]; P = .04). The rate of in-hospital mortality was 24% in the helmet group and 25% in the high-flow nasal oxygen group (absolute difference, −1% [95% CI, −17% to 15%]; P > .99).
- CONCLUSIONS & RELEVANCE: Among pts with COVID-19 and moderate to severe hypoxemia, treatment with helmet noninvasive ventilation, compared with high-flow nasal O2, resulted in no significant difference in the number of days free of respiratory support within 28 days but significantly fewer HELMET pts required intubation or mechanical ventilation.

PREVENTION/ MITIGATION

Butler-Laporte G, Lawandi A, Schiller I et al. **Comparison of Saliva and Nasopharyngeal Swab Nucleic Acid Amplification Testing for Detection of SARS-CoV-2:** A Systematic Review and Meta-analysis. JAMA Intern Med. Published online January 15, 2021. **doi:10.1001/jamainternmed.2020.8876**.

- To assess the diagnostic accuracy of saliva NAAT for COVID-19, a systematic review of was performed, using all studies with enough data to measure salivary NAAT sensitivity and specificity.
- Results were compared with the standard, imperfect nasopharyngeal swab NAAT as a reference test. To account for the imperfect reference test sensitivity, a Bayesian latent class bivariate model was used for the meta-analysis.
- The search strategy yielded 385 references, and 16 unique studies were identified for quantitative synthesis. Ultimately, 8 peer-reviewed studies and 8 preprints were included in the meta-analyses (5922 unique pts). There was significant variability in pt selection, with 15 studies including ambulatory pts, and 9 exclusively enrolled from an outpatient population with mild or no symptoms.
- RESULTS: In the primary analysis, the saliva NAAT pooled sensitivity was 83.2% (95% credible interval [CrI], 74.7%-91.4%) and the pooled specificity was 99.2% (95% CrI, 98.2%-99.8%). The nasopharyngeal swab NAAT had a sensitivity of 84.8% (95% CrI,76.8%-92.4%) and a specificity of 98.9% (95% CrI, 97.4%-99.8%). Results were similar in secondary analyses.
- CONCLUSIONS: These results suggest that saliva NAAT diagnostic accuracy is similar to that of nasopharyngeal swab NAAT, especially in the ambulatory setting. These findings support larger-scale research on the use of saliva NAAT as an alternative to nasopharyngeal swabs.

****

Wu K, Werner AP, Moliva JI et al. **mRNA-1273 vaccine induces neutralizing antibodies against spike mutants from global SARS-CoV-2 variants**. bioRxiv preprint. **doi: https://doi.org/10.1101/2021.01.25.427948**; January 25, 2021

- Moderna's SARS-CoV-2 vaccine, mRNA-1273, elicits high viral neutralizing titers in Phase 1 trial participants and is highly efficacious in prevention of symptomatic & severe COVID-19 disease.
- To assess the efficacy of the vaccine against SARS-CoV-2 variants with mutations in the spike protein, most recently circulating isolates from the UK (B.1.1.7) and South Africa (B.1.351), neutralization of sera from mRNA-1273 vaccinated clinical trial participants against recombinant VSV-based SARS-CoV-2 PsVN assay with S protein from the original Wuhan-Hu-1 isolate, D614G variant, the B.1.1.7 and B.1.351 variants was assessed.
- Results demonstrate that the antibody response elicited by mRNA-1273 provides similar levels of neutralization against these SARS-CoV-2 S variants as against the Wuhan-Hu-1 (D614) strain.

- The mutations present in the B.1.1.7 variant (UK), either the complete set of S mutations or thespecific mutations (N501Y, ΔH69ΔV70) of key interest had no significant effect on neutralization in any assay. In contrast, a significant decrease in neutralizing titers was measured against both the full set of S mutations and the partial list of RBD mutations in the B.1.351 variant(South Africa).
  → CONCLUSION: mRNA-1273 maintained activity against all circulating strain variants tested to date, and only the B.1.351 variant showed reduced neutralizing titers, as assessed from vaccinated human and NHP sera.

****

Logunov DY, Dolzhikova IV, Shcheblyakov DV et al. **Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomized controlled phase 3 trial in Russia.** The Lancet. February 02, 2021 **DOI:https://doi.org/10.1016/S0140-6736(21)00234-8**

- A heterologous recombinant adenovirus (rAd)-based vaccine, Gam-COVID-Vac (Sputnik V), showed a good safety profile and induced strong humoral and cellular immune responses in participants in phase 1/2 clinical trials. Here, we report preliminary results on the efficacy and safety of Gam-COVID-Vac from the interim analysis of this phase 3 trial.
- A randomized, double-blind, placebo-controlled, phase 3 trial was performed at 25 hospitals and polyclinics in Moscow, Russia. Participants were randomly assigned (3:1) to receive vaccine or placebo, with stratification by age group. The vaccine was administered (0·5 mL/dose) intramuscularly in a prime-boost regimen: a 21-day interval between the first dose (rAd26) and the second dose (rAd5), both vectors carrying the gene for the full-length SARS-CoV-2 glycoprotein S.
- The primary outcome was the proportion of participants with PCR-confirmed COVID-19 from day 21 after receiving the first dose. Serious adverse events were assessed in all participants who had received at least one dose at the time of database lock, and rare adverse events were assessed in all participants who had received two doses.
- RESULTS: Between Sept 7 and Nov 24, 2020, 21 977 adults were randomly assigned to the vaccine group (n=16 501) or the placebo group (n=5476). 19 866 received two doses of vaccine or placebo and were included in the primary outcome analysis. From 21 days after the first dose of vaccine (the day of dose 2), 16 (0·1%) of 14 964 participants in the vaccine group and 62 (1·3%) of 4902 in the placebo group were confirmed to have COVID-19; vaccine efficacy was 91·6% (95% CI 85·6–95·2).
- Adverse events occurred at the same frequency in both groups.
- CONCLUSION: This interim analysis of the phase 3 trial of Gam-COVID-Vac showed 91·6% efficacy against COVID-19; the vaccine was well tolerated in a large cohort.

****

Hall V, Foulkes S, Charlett A et al. **Do antibody positive healthcare workers have lower SARS-CoV-2 infection rates than antibody negative healthcare workers? Large multi-centre prospective cohort study (the SIREN study), England: June to November 2020.** MedRXiv; Published Jan 15, 2021. **https://doi.org/10.1101/2021.01.13.21249642.**

- To assess duration & protection of antibodies to SARS-CoV-2, PCR, antibody (Ab) testing & clinical F/U for COVID-19 were performed prospectively every 2-4 weeks in 20,787 volunteers. At enrolment, participants were assigned to either the positive cohort (Ab positive or prior PCR/Ab test positive) or negative cohort (Ab negative, not previously known to be PCR/Ab positive).
- FINDINGS: Between 6/18 & 9/11/2020, 44 reinfections (2 probable, 42 possible) were detected in the baseline positive cohort of 6,614 participants, collectively contributing 1,339,078 days of follow-up. This compares with 318 new PCR positive infections and 94 antibody seroconversions in the negative cohort of 14,173 participants, contributing 1,868,646 days of follow-up.
- The incidence density per 100,000 person days was 3.3 reinfections in the positive cohort, compared with 22.4 new PCR confirmed infections in the negative cohort. The adjusted odds ratio was 0.17 for all reinfections (95% CI 0.13-0.24) compared to PCR confirmed primary infections. The median interval between primary infection and reinfection was over 160 days.
- → A prior history of SARS-CoV-2 infection was associated with an 83% lower risk of infection, with median protective effect observed five months following primary infection.

****

Brooks JT, Beezhold DH, Noti JD, et al. **Maximizing Fit for Cloth and Medical Procedure Masks to Improve Performance and Reduce SARS-CoV-2 Transmission and Exposure, 2021.** MMWR Morb Mortal Wkly Rep. ePub: 10 February 2021. DOI: http://dx.doi.org/10.15585/mmwr.mm7007e1.

- To evaluate changes in mask fit to improve performance, the CDC assessed the impact of 1) double masking and 2) knotting and tucking the medical procedure mask, on the amount of particles emitted during a cough.
- A pliable elastomeric headform was used to simulate a person coughing by producing aerosols from a mouthpiece. The effectiveness of three mask configurations to block these aerosols was assessed: a three-ply medical procedure mask alone, a three-ply cloth cotton mask alone, and the three-ply cloth mask covering the three-ply medical procedure mask (double masking).
- The second experiment assessed how effectively the two modifications to medical procedure masks reduced exposure to aerosols emitted during a period of breathing. Ten mask combinations, using various configurations of no mask, double masks, and unknotted or knotted and tucked medical procedure masks, were assessed.
- A knotted and tucked medical procedure mask is created by bringing together the corners and ear loops on each side, knotting the ears loops together where they attach to the mask, and then tucking in and flattening the resulting extra mask material to minimize the side gaps.
- A modified simulator with two pliable elastomeric headforms (a source and a receiver) was used to simulate the receiver's exposure to aerosols produced by the source during quiet breathing, light work, & moderate work. For each masking configurations, three 15-minute runs were completed.
- RESULTS: The first experiment demonstrated that the unknotted medical procedure mask alone blocked 42.0% of the particles from a simulated cough (standard deviation [SD] = 6.70), and the cloth mask alone blocked 44.3% (SD = 14.0). The combination of the cloth

mask covering the medical procedure mask (double mask) blocked 92.5% of the cough particles (SD = 1.9).

- In the second experiment, adding a cloth mask over the source medical procedure mask or knotting and tucking the medical procedure mask reduced the cumulative exposure of the unmasked receiver by 82.2% (SD = 0.16) and 62.9% (SD = 0.08), respectively. When the source was unmasked and the receiver was fitted with the double mask or the knotted and tucked medical procedure mask, the receiver's cumulative exposure was reduced by 83.0% (SD = 0.15) and 64.5% (SD = 0.03), respectively. When the source and receiver were both fitted with double masks or knotted and tucked masks, the cumulative exposure of the receiver was reduced 96.4% (SD = 0.02) and 95.9% (SD = 0.02), respectively.

****

Voysey M, Costa C, Madhi SA et al. Shabir A. **Single dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) Vaccine.** The Lancet Preprints, January 2021. **https://ssrn.com/abstract=3777268**

- The timing of the booster dose of Astra Zeneca's CoV-19 vaccine is important because proof that a longer delay does not affect immunogenicity would free up doses for use as primers when COVID-19 vaccines are in short supply. This analysis of the AZD1222 vaccine trial evaluates immunogenicity when the booster dose is given after 12 weeks.
- RESULTS: (1) The primary analysis of overall vaccine efficacy >14 days after the second dose based on the prespecified criteria was 66.7% (57.4%, 74.0%). There were no hospitalizations in the ChAdOx1 nCoV-19 group after the initial 21 day exclusion period, and 15 in the control group. (2) Vaccine efficacy after a single standard dose of vaccine from day 22 to day 90 post vaccination was 76% (59%, 86%), and protection did not wane during this initial 3 month period. These observations are supported by immunogenicity data which showed binding antibody responses more than 2-fold higher after an interval of 12 or more weeks compared with and interval of less than 6 weeks GMR 2.19 (2.12, 2.26) in those who were 18-55 years of age. Analysis of weekly nasal cultures for SARS-CoV-2 showed overall cases of any PCR+ were reduced by 67% (95%CI 49%, 78%) after a single SD vaccine suggesting the potential for a substantial reduction in transmission
- CONCLUSION: With ChAdOx1 nCoV-19 higher vaccine efficacy is obtained with a longer interval between the first and second dose, and a single dose of vaccine is highly efficacious in the first 90 days. Preliminary data also suggest the potential for a substantial reduction in transmission.

****

Levine-Tiefenbrun M, Yelin I, Katz R et al. **Decreased SARS-CoV-2 viral load following vaccination.** medRxiv 2021; posted Feb 8, 2021. https://doi.org/10.1101/2021.02.06.21251283.

- To analyze the effect of vaccination on viral loads in COVID-19 post-vaccination, we retrospectively collected and analyzed the RT-qPCR test measurements of the 3 viral genes, E, N and RdRp for positive post-vaccination tests performed between December 23rd 2020 and January 25th 2021 (n=2,897 patients)
- Results in vaccinated subjects were compared to results in unvaccinated subjects during the same time period, matched for age and sex.

- Viral load was significantly lower in vaccinated subjects beginning 12 days or longer post vaccination.
- Analyzing positive SARS-CoV-2 test results following vaccination, we find that the viral load is reduced 4-fold for infections occurring 12-28 days after the first dose of vaccine. These reduced viral loads support lower infectiousness, further contributing to vaccine impact on virus spread.
- CONCLUSION: Results show that infections occurring 12 days or longer following vaccination have significantly reduced viral loads, potentially affecting viral shedding and contagiousness as well as severity of disease.

****

KIM H, Hegde S, LaFiur C et al. **Access to personal protective equipment in exposed healthcare workers and COVID-19 illness, severity, symptoms and duration: a population-based case-control study in six countries.** BMJ Glob Health. 2021; 6(1): e004611. Published online 1/28/2021.
doi: 10.1136/bmjgh-2020-004611

- To assess the risk, severity & duration of COVID-19 in relation to access to PPE, at-risk healthcare workers (HCWs) (physicians & nurses) from a provider network in 6 countries (the UK, Germany, France, Italy, Spain, USA) were identified based on adult medical specialties with frequent & close contact with pts with COVID-19.
- Exposed HCWs completed a detailed questionnaire including demographics, medical, social and lifestyle factors. COVID-19 cases were defined as COVID-19 symptoms (fever, cough, fatigue, loss of taste or smell) and asymptomatic COVID-19 test positive cases.
- RESULTS: Among 2884 exposed HCWs (94% MDs/6% RNs/PAs), there were 514 reports of COVID-19 illness and 54 asymptomatic COVID-19 test positive cases. COVID-19 risk was significantly associated with close contact with COVID-19 cases in & outside the workplace, number of work shifts and hours worked per week.
- Limited access to PPE compared with access to a fresh mask, gown, gloves & face shield with each pt encounter was associated with a 2.2-fold to 22-fold increased risk of reporting COVID-19 symptoms ($p<0.0001$), a pattern consistent across all six countries.
- Limited access to PPE was associated with symptom duration greater than 2 weeks & the presence of moderate to severe symptoms such as difficulty breathing, abnormal chest X-ray, low oxygen saturations, respiratory distress and acute lung injury.
- CONCLUSION: In six countries, less access to PPE was strongly associated with increased risk of reporting COVID-19 illness & more prolonged & severe disease course in frontline HCWs.

****

Van den Berg P, Schecter-Perkins EM, Jack RS et al. **Effectiveness of three versus six feet of physical distancing for controlling spread of COVID-19 among primary and secondary students and staff: A retrospective, state-wide cohort study.** Clinical Infectious Diseases, March 10,2021. https://doi.org/10.1093/cid/ciab230

- STUDY DESIGN: Community incidence rates of SARS-CoV-2, SARS-CoV-2 cases among students in grades K-12 and staff participating in-person learning and district infection control plans were linked. Incidence rate ratios (IRR) for students and staff members in districts with

≥3 versus **≥6** feet of physical distancing were estimated using log-binomial regression; models adjusted for community incidence are also reported.

- RESULTS: Among 251 eligible school districts, 537,336 students and 99,390 staff attended in-person instruction during the 16-week study period, representing 6,400,175 student learning weeks and 1,342,574 staff learning weeks. Student case rates were similar in the 242 districts with ≥3 feet versus ≥6 feet of physical distancing between students (IRR, 0.891, 95% CI, 0.594-1.335); results were similar after adjusting for community incidence (adjusted IRR, 0.904, 95% CI, 0.616-1.325). Cases among school staff in districts with ≥3 feet versus ≥6 feet of physical distancing were also similar (IRR, 1.015, 95% CI, 0.754-1.365).
- CONCLUSIONS: Lower physical distancing policies can be adopted in school settings with masking mandates without negatively impacting student or staff safety.

****

Thompson MG, Burgess JL, Naleway AL et al. I**nterim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Health Care Personnel, First Responders, and Other Essential and Frontline Workers — Eight U.S. Locations, December 2020–March 2021**. MMWR 2021; Early Release/ March 29, 2021. **http://dx.doi.org/10.15585/mmwr.mm7013e3**

- Prospective cohorts of 3,950 health care personnel, first responders, and other essential and frontline workers who had received m-RNA vaccines against SARS-CoV-2 infection completed weekly SARS-CoV-2 testing for 13 consecutive weeks regardless of symptoms.
- Among participants with no previous laboratory documentation of SARS-CoV-2 infection, 2,479/3950 (62.8%) received both recommended mRNA doses & 477/3950 (12.1%) received only 1 dose of mRNA vaccine.
- RESULTS: Among unvaccinated participants, 1.38 SARS-CoV-2 infections were confirmed by reverse transcription–polymerase chain reaction (RT-PCR) per 1,000 person-days. 58% of infections were detected before people had symptoms. 10.2% of infected people never developed symptoms.
- By contrast, among fully immunized (≥14 days after second dose) persons, 0.04 infections per 1,000 person-days were reported, and among partially immunized (≥14 days after first dose and before second dose) persons, 0.19 infections per 1,000 person-days were reported.
- Troubling variants were circulating during the time of the study — from Dec. 14, 2020, to March 13, 2021 — yet the vaccines still provided powerful protection.
- CONCLUSION: Estimated mRNA vaccine effectiveness for prevention of infection, adjusted for study site, was 90% for full immunization and 80% for partial immunization. Authorized mRNA COVID-19 vaccines (Pfizer-BioNTech's BNT162b2 and Moderna's mRNA-1273) are highly effective in real-world conditions.

****

Madhi SA, Baillie V, Cutland CL et al. **Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant.** New Engl J Med. March 16, 2021; **DOI: 10.1056/NEJMoa2102214.**

- A multicenter, double-blind RCT was conducted in South Africa between 6 & 11/2020, involving 750 vaccine recipients and 717 placebo recipients. Individuals received two doses, 21 to 35 days apart.
- During the ascertainment period, 42 individuals developed mild to moderate COVID-19, and 39 (93%) of these cases were attributed to the B.1.351 variant.
- Serological studies in a small subset of participants demonstrated greatly reduced live virus neutralization of the B.1.351 variant compared with the original SARS-CoV-2 strain.
- The vaccine showed almost no efficacy for prevention of mild to moderate COVID-19 in this trial (VE: 21.9%; 95% CI: −49.9–59.8). When limited to only B.1.351 cases, the estimated vaccine efficacy was 10.4% (−76.8–54.8).
- CONCLUSIONS: A two-dose regimen of the ChAdOx1 nCoV-19 vaccine did not show protection against mild-to-moderate Covid-19 due to the B.1.351 variant.