Summary of Major Literature Related to COVID-19 (August 25, 2021)

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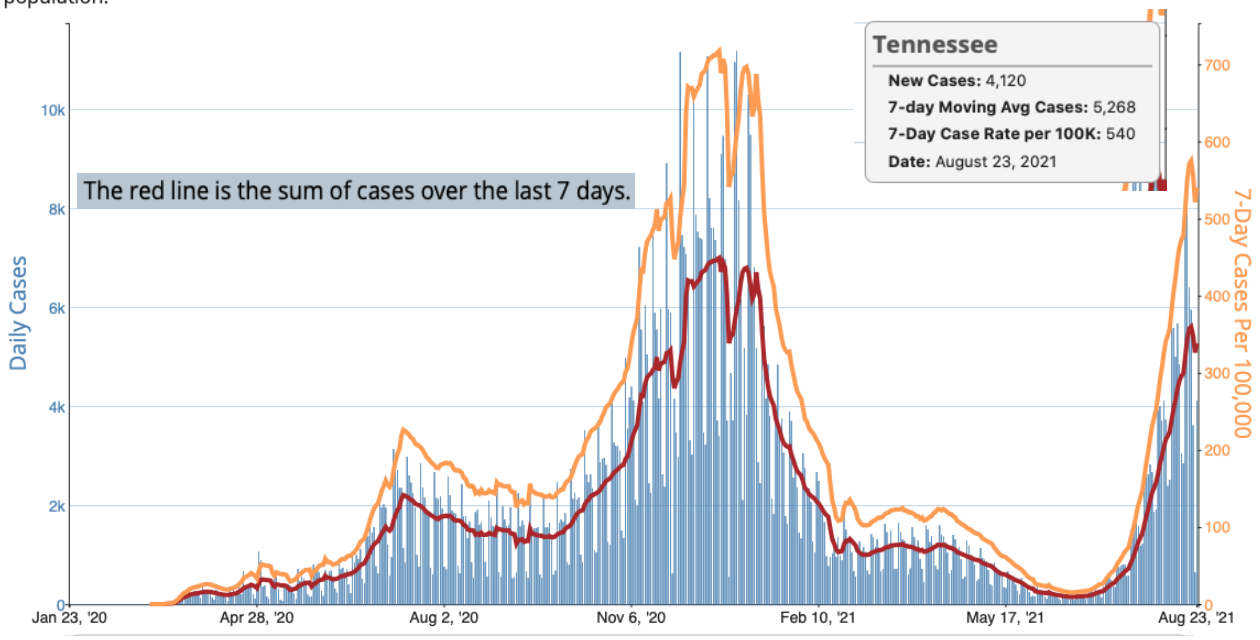
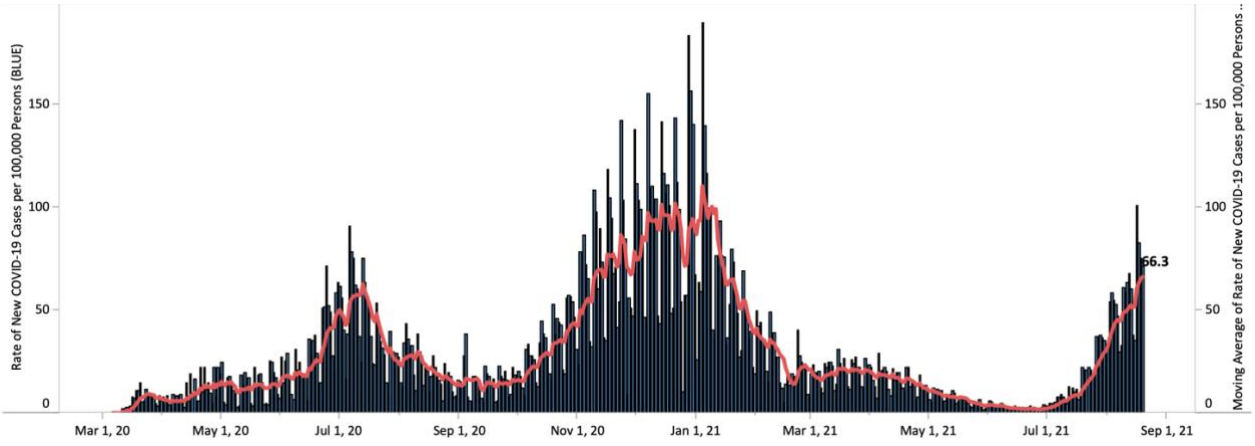
***This is informational and not intended to create variance from VUMC policies/guidance**

Tennessee

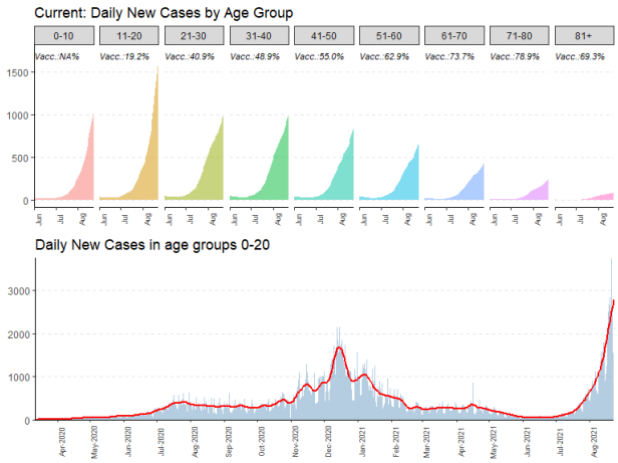
Daily Trends in Number of Cases and 7-Day Cumulative Incidence Rate of COVID-19 Cases in Tennessee Reported to CDC, per 100,000 population.



Davidson county



Cases by age, TN (Courtesy @DrJMLuther)



TREATMENT

Anticoagulation

1. **Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19.** The ATTACC, ACTIV-4a, and REMAP-CAP Investigators. NEJM. 4 Aug 2021.

- An international, open-label, adaptive, multiplatform, randomized controlled trial among non-critically ill hospitalized COVID-19 patients (without the need for ICU-level cardiovascular or respiratory organ support at enrollment) to examine whether initial therapeutic-dose anticoagulation with heparin improves in-hospital survival and reduces the duration of organ support compared to usual-care pharmacologic thromboprophylaxis
- Primary outcome: organ support-free days
    - Ordinal scale that combined in-hospital death and number of days free of cardiovascular or respiratory organ support up to Day 21 for those who survived to discharge
- Primary analysis population was 2219 patients, 1048 in usual-care thromboprophylaxis arm and 1171 in therapeutic-dose anticoagulation arm
    - Further stratification according to baseline D-dimer level as high (≥2 times upper limit of normal), low (<2 times upper limit of normal) or unknown
- Overall, the probability that therapeutic-dose anticoagulation increased organ support–free days as compared with usual-care thromboprophylaxis was 98.6% (adjusted odds ratio 1.27; 95% CI, 1.03-1.58)
    - Probability of superiority was 97.3%, 92.9% and 97.3% in high, low, and unknown D-dimer groups, respectively
- 76.4% of usual-care group vs. 80.2% of therapeutic-dose anticoagulation group survived until hospital discharge without organ support (median adjusted absolute difference 4.0%; 95% CI 0.5-7.2)
- Major bleeding occurred more frequently in the anticoagulation group (1.9% vs. 0.9%)
- Implications: In noncritically ill patients hospitalized with COVID-19, an initial strategy of therapeutic-dose anticoagulation with heparin increased the probability of survival until hospital discharge with reduced need for organ support as compared with usual-care thromboprophylaxis; Benefit was observed regardless of baseline D-dimer level, but was most pronounced in the high D-dimer cohort, which was older and had higher prevalence of comorbidities

Convalescent Plasma

2. **Early Convalescent Plasma for High-Risk Outpatients with Covid-19**. Korley et al. NEJM. 18 Aug 2021.

- Randomized, multicenter, single-blind trial; all patients (511) presented to ED with symptoms (stable for outpatient management), >50 yo with at least 1 risk factor within 7d of symptom onset; received either 1 unit of high titer convalescent plasma (nAb 1:641) or placebo
- Primary outcome: Disease progression within 15 days after randomization, which was a composite of hospital admission for any reason, seeking emergency or urgent care, or death without hospitalization
    - Disease progression occurred in 77 patients (30.0%) in the convalescent-plasma group (CPG) and in 81 patients (31.9%) in the placebo group (PG) (risk difference, 1.9 percentage points; 95% CI, −6.0 to 9.8; posterior probability of superiority of convalescent plasma, 0.68).
- There was no association between Ab titer and disease progression
- Five patients in the CPG and 1 patient in the PG died.
- Outcomes regarding worst illness severity and hospital-free days (28.3 d CPG v 28.6 d PP) were similar in the two groups; worsening of symptoms was reported in 41.6% CPG and 45.7% in the PG.
- Dyspnea occurred more often in the PG; and infusion-related reactions, which occurred more often in the CPG; all other adverse events occurred with similar frequency
- Implications: administration of high-titer Covid-19 convalescent plasma to high-risk outpatients within 1 week after the onset of symptoms of Covid-19 did not prevent disease progression; results are

consistent with RCTs among hospitalized patients that also showed no improvement in clinical outcome in those who received convalescent plasma

- Also see: JAMA 2020;324:460-470, BMJ 2020;371:m3939-m3939, NEJM 2021;384:619-629

VACCINES

Safety

3. **Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting.** Barda et al. NEJM. 25 Aug 2021.

- Large real-world safety study of short- and medium-term adverse side effects associated with Pfizer-BioNTech vaccine was conducted in Israel
    - Examined incidence of adverse events in vaccinated vs matched unvaccinated individuals (average N=884,828 in each group), and also examined the same adverse events in SARS-CoV-2 infected individuals vs. an uninfected control group (average N=173,106 in each group)
    - For each comparison, controls were matched on sociodemographic and clinical variables that may influence vaccination and/or development of adverse events
    - Calculated risk ratios and risk differences at 42 days after vaccination (or COVID-19 diagnosis)
- Vaccination analysis
    - Compared to the unvaccinated control group, vaccination was associated with an elevated risk of myocarditis (risk ratio, 3.24; 95% CI, 1.55 to 12.44; risk difference, 2.7 events per 100,000 persons; 95% CI, 1.0 to 4.6), lymphadenopathy (risk ratio, 2.43; 95% CI, 2.05 to 2.78; risk difference, 78.4 events per 100,000 persons; 95% CI, 64.1 to 89.3), appendicitis (risk ratio, 1.40; 95% CI, 1.02 to 2.01; risk difference, 5.0 events per 100,000 persons; 95% CI, 0.3 to 9.9), and herpes zoster infection (risk ratio, 1.43; 95% CI, 1.20 to 1.73; risk difference, 15.8 events per 100,000 persons; 95% CI, 8.2 to 24.2)
    - Median age of 21 cases of myocarditis in vaccinated group was 25 years (IQR, 20-34) and 90.9% were male
- Infection analysis
    - SARS-CoV-2 infection was associated with a substantially increased risk of myocarditis (risk ratio, 18.28; 95% CI, 3.95 to 25.12; risk difference, 11.0 events per 100,000 persons; 95% CI, 5.6 to 15.8)
    - SARS-CoV-2 infection substantially increased risk for numerous additional serious adverse events for which vaccination did not increase risk, including pericarditis, acute kidney injury, arrhythmia, deep-vein thrombosis, pulmonary embolism, myocardial infarction, intracranial hemorrhage, and thrombocytopenia

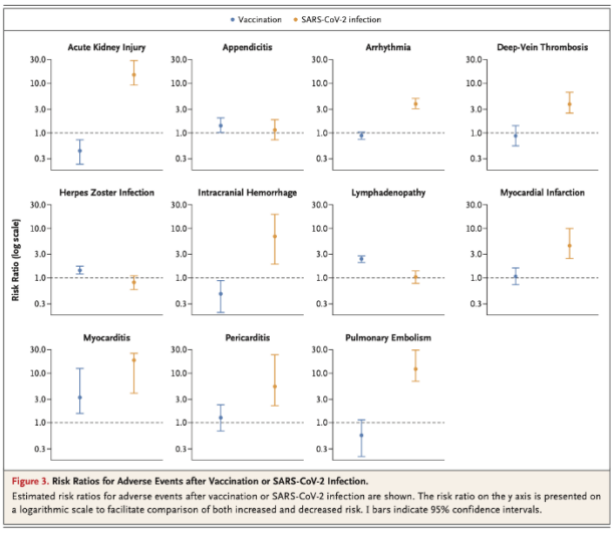


Figure 3. Risk Ratios for Adverse Events after Vaccination or SARS-CoV-2 Infection.
Estimated risk ratios for adverse events after vaccination or SARS-CoV-2 infection are shown. The risk ratio on the y axis is presented on a logarithmic scale to facilitate comparison of both increased and decreased risk. I bars indicate 95% confidence intervals.

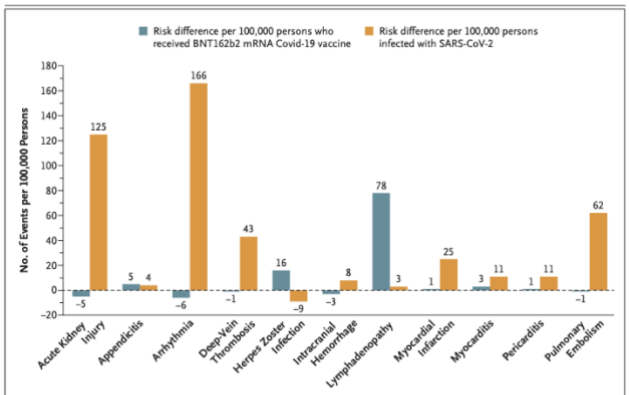


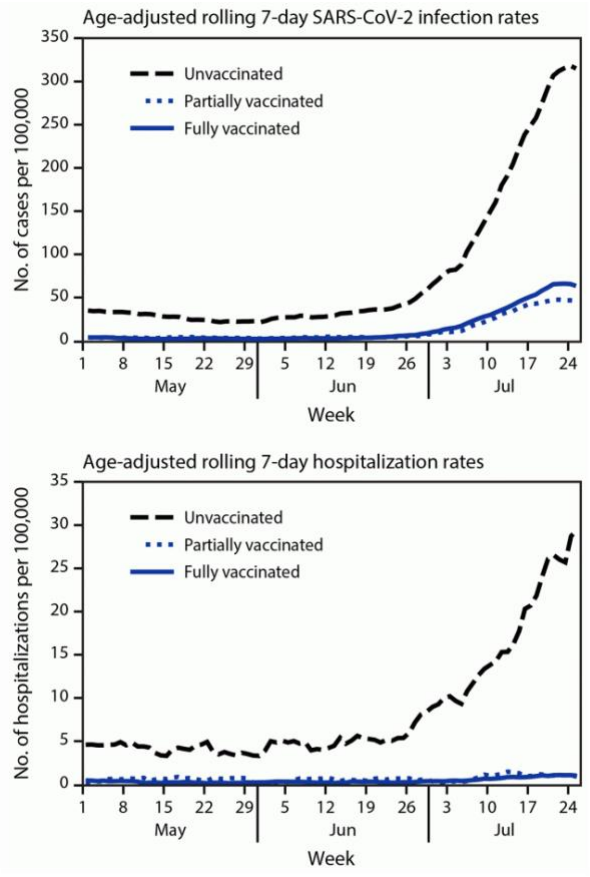
Figure 4. Absolute Excess Risk of Various Adverse Events after Vaccination or SARS-CoV-2 Infection.
Point estimates of the risk differences for selected adverse events are shown. Estimates were derived 42 days after vaccination or SARS-CoV-2 infection with the use of the Kaplan–Meier estimator. Risk differences are shown per 100,000 persons and rounded to the nearest integer. Negative differences (decreased risk) are represented as negative values on the y axis, and positive differences (increased risk) are represented as positive values on the y axis. The abbreviation mRNA denotes messenger RNA.

- Limitations: Excluded long term care facility residents and health care workers, limiting generalizability; median age in vaccination analysis (38y) and infection analysis (34y) was younger than eligible population; observational study so potential for confounding; uncertain probability of infection; additional adverse effects of SARS-CoV-2 infection including long-term effects are not considered
- Implications: Well-designed target trial in a nationwide mass vaccination setting provides evidence of safety for Pfizer-BioNTech vaccine; small increased risk of a few adverse events, including myocarditis, after vaccination was lower than that associated with COVID, which also substantially increased risk for numerous other serious adverse events

Efficacy/effectiveness

4. **Effectiveness of COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Frontline Workers Before and During B.1.617.2 (Delta) Variant Predominance — Eight U.S. Locations, December 2020–August 2021.** Fowlkes et al. MMWR. 24 Aug 2021.

- Interim updated analysis of vaccine effectiveness (VE) from Dec 14, 2020 to August 14, 2021 in HEROES-RECOVER, a network of prospective cohorts among frontline workers including HCW, first responders, other essential workers
  - Weekly PCR testing for SARS-CoV-2 infection
- 3483/4217 participants (83%) were vaccinated
  - 65% Pfizer-BioNTech, 33% Moderna, 2% J&J
- Overall adjusted VE against infection was 80% (95% CI, 69-88%), based on 194 infections (89.7% symptomatic) during unvaccinated person-time and 34 infections (80.6% symptomatic) during vaccinated person-time
- No statistically significant difference in VE by time since completion of vaccination
  - 85% for <120 days since completion and 73% for ≥150 days with overlapping confidence intervals



- VE decreased from 91% (81-96%) before Delta variant predominance to 66% (26-84%) during Delta predominance weeks
- Limitations: Did not examine VE against severe illness or hospitalization; Unable to disentangle effect of time since vaccination from that of Delta variant; small number of infections and imprecise estimates, especially for Delta predominant time period; data not presented separately by vaccine
- Implications: Vaccines continue to provide strong protection against infection, but a reduction in VE over time has been observed
- See also: **SARS-CoV-2 Infections and Hospitalizations Among Persons Aged ≥16 Years, by Vaccination Status — Los Angeles County, California, May 1–July 25, 2021**. Griffin et al. MMWR. 24 Aug 2021.
- Linked case surveillance and vaccination registry data
- Similar pattern in LA County as that observed in other US counties and states during period of rise in Delta predominance and increasing time since vaccination
- Age-adjusted infection and hospitalization rates by vaccination status (**see Figure**) show 4.9 times higher

incidence and 29.4 times higher hospitalization rate in unvaccinated compared to fully vaccinated individuals

- Lower percentages of fully vaccinated people were admitted to an ICU unit, required mechanical ventilation, or died compared to unvaccinated
- Among individuals hospitalized or admitted to an ICU, median age was significantly older among vaccinated (64 years and 64 years, respectively) than unvaccinated individuals (49 years and 56 years, respectively)
- Implication: Vaccines provide strong and consistent protection against hospitalization

Animal models

5. **mRNA-1273 protects against SARS-CoV-2 beta infection in nonhuman primates.** Corbett. Nature Immunology. 20 Aug 2021.

- Nonhuman primates (NHP) were given one of 3 mRNA-1273 (Moderna) dosing regimens or no vaccine (One 30ug dose, two 30ug doses, or two 100ug doses, 4 weeks apart).
- The levels of neutralizing Ab (nAb) were measured at week 12 using several neuralization assays (comparing SARS-CoV2 pAsp614Gly, Alpha, Beta and Gamma VOC); in general, 2 doses gave higher neutralizing activity than single dose
    - prime/boost lead to >10^3 reciprocal 50% inhibitory dose (ID50) in nearly all animals against pAsp614Gly but only ~75% of animals had detectable nAb against the Beta VOC ; the 1 dose regimen (30ug) only lead to 75% of animals developing nAb against pAsp614Gly and no nAb detected against the Beta VOC
    - little change comparing p.Asp614Gly to Alpha
    - reduced neutralization was observed against the Gamma VOC (P.1, similar to Beta VOC)
    - reduced neutralizing responses against Delta VOC (B.1.617.2) [3-fold lower than activity observed with the reference (p-Asp614Gly)]
- S-specific and RBD-specific IgG were measured in the sera by Multi-array ELISA (WA-1 v. Alpha, Beta, Gamma)
    - S-specific and RBD-specific Ab levels were 2-3 fold lower against the Beta variant Spike compared to the WA-1 Spike (which the vaccine spike); differences were vaccine dose regimen dependent;
- At ~3 wks after boost or 7 wks after the single 30-µg; there was a dose-dependent increase in BAL and nasal wash WA-1 or B.1.351 S-specific IgG and IgA, BAL WA-1 or B.1.351 S-specific IgA responses in nasal wash samples trended higher only in the two-dose vaccine groups compared to control NHPs (RBD-specific Ab followed a similar pattern).
- S-specific Th1 responses (T cells expressing interferon (IFN)-γ, IL-2 or tumor necrosis factor) were induced in a dose-dependent manner; low to undetectable TH2 cell responses (expressing IL-4 or IL-13) in all groups; frequency of S-specific TFH responses (expressing CXCR5+ PD-1+ICOS+ CD4+ T cells and CD40L or IL-21) was dose dependent; S-specific CD8+ T cell responses were observed in five of eight NHPs that received two doses of 100 µg mRNA-1273
- 7-8 weeks post boost (or 12 wk post single dose) intratracheal and intranasal challenges with performed with total dose of 5×10^5 PFUs of Beta VOC (B.1.351)
    - significant reduction and faster control of B.1.351 viral replication in the lower airways following vaccination; control (but relatively more limited) in the upper airway only occurred in high dose, 2 dose group
    - virus-related pathology and the detection of viral antigen were assessed in the lung 8 d post challenge; the range of severity of inflammation was similar between vaccination groups;

antigen was detected in all unvaccinated animals; ½ of NHP receiving 1 dose of vaccine and non of the animals receiving 2 doses
    - Antibody responses and CD8+ T cell responses increased in the BAL and nasal swabs only in NHP which had viral replication (unvaccinated and 1 dose vaccine group) 14 d post challenge- No increase in CD4+ T cells at the time assessed
- At time of challenge (12 weeks post boost) Beta (B.1.351) S-specific IgG antibody titers also correlated strongly with reduction of sgRNA in both BAL and NS samples at day 2 after challenge (defined by authors as antibody correlates of protection)
- Limitations: Study authors suggest challenge with Delta VOC is underway; these challenge data focus on Beta VOC; pathological response is limited in the NHP; small sample sizes make statistical analyses difficult
- Implications: 2, high dose regimen of mRNA-1273 vaccine can provide upper and lower airway protection against a major variant of concern (Beta); may imply NHP challenged with other VOC (for which the sera had neutralizing activity against based on their findings) would also be protected

IMMUNE RESPONSE

6. **Naturally enhanced neutralizing breadth against SARS-CoV-2 one year after infection.** Wang et al. Nature. 14 June 2021.

- Antibody responses were assessed in a cohort of 63 individuals who have recovered from COVID-19 (1.3, 6.2 and 12 months after infection); 41% were also vaccinated with an mRNA vaccine.
    - Subjects had diverse disease course; 10% hospitalized; 14% reported persistent symptoms at 1 yr; 44% reported persistent symptoms at 6mo;
    - Symptom persistence was not associated with the duration and severity of acute disease or with vaccination status: anti-N antibody titers decreased significantly between 6-12 months in all individuals (ELISA)
- In unvaccinated individuals, Ab reactivity to the receptor binding domain (RBD) of SARS-CoV-2 (ELISA), neutralizing activity and the # RBD-specific memory B cells were 'relatively' stable over 6 -12 months
- IgG titers increased ~30-fold in vaccinated compared with unvaccinated in this cohort of previously infected individuals
    - Vaccination serum neutralizing activities against variants of concern ≥ the activity against the original Hu-1 strain (relative to vaccinated, naïve individuals or unvaccinated, previously infected) (these assays performed with HIV-1 virus pseudotyped with the S protein from Alpha, Beta, Gamma or Iota)
    - Evidence of Ab somatic mutation, memory B cell clonal turnover and development of mAbs resistant to SARS-CoV-2 RBD mutations
    - B cell clones expressing broad and potent antibodies are selectively retained in the repertoire over time and expand markedly after vaccination.
- Limitations: Small cohort; whether these Ab generated are correlates of protection is not clear; no analysis of the activity against the Delta variant's S protein
- Implications: B cell immunity in convalescent individuals will be very long lasting; convalescent individuals who receive available mRNA vaccines will produce antibodies and memory B cells that broadly neutralized pseudotyped viruses with several different variants' S proteins.

ORIGIN OF THE VIRUS

7. **The Origins of SARS-CoV-2: A Critical Review**. Holmes et al. Cell. 19 Aug 2021 (in press).

- A group of researchers associated with 22 institutions have written a review to critically review the currently available scientific evidence about the origin of SARS-CoV-2. They review rationale for the

explanation that the origin of SARS-CoV-2 is a zoonotic event and further, they highlight the lack of evidence that it is of laboratory origin.

- All previous human coronaviruses have zoonotic origins, as have the vast majority of human viruses
- The Huanan market in Wuhan was an early epicenter of SARS-CoV-2 infection; while no epidemiological link to any other locality in Wuhan, including the Wuhan Institute of Virology (WIV)
- Many thousands of live wild animals (including high-risk species - civets and raccoon dogs) were traded in the Huanan market; SARS-CoV-2 was detected in environmental samples where trades done
- As more CoV viruses are sequenced, its clear that RaTG13 (the bat virus collected by WIV) is NOT the progenitor of SARS-CoV-2 (with or without manipulation or experimental mutagenesis)
- No reported SARS-CoV-2 cases related to any laboratory staff at the WIV (all seronegative in March 2020); laboratory found to follow biosafety protocols; while WIV has CoVs – few have been successfully grown in culture and those that have are not closely related to SARS-CoV-2 (RaTG13 was not isolated nor cultured- segments of its genome were sequenced).
- Limitations impacting the ability to find the exact origin: high rates of asymptomatic transmission and undocumented secondary transmission events, animals tested for SARS-CoV-2 underrepresented previously identified high-risk species, need for coordinated, funded efforts, the passage of time and the time required