Archived Editions (COVID-19 Genomics and Precision Public Health Weekly Update)

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COVID-19 Genomics and Precision Public Health Weekly Update Content

- Pathogen and Human Genomics Studies
- News, Reviews and Commentaries

Pathogen and Human Genomics Studies

- Relative Effectiveness of Four Doses Compared to Three Dose of the BNT162b2 Vaccine in Israel (https://www.medrxiv.org/content/10.1101/2022.03.24.22272835v1)
  S Gazit et al, MEDRXIV, March 24, 2022

  A fourth dose provided considerable additional protection against both SARS-CoV-2 infection and severe disease relative to three doses of the vaccine. However, vaccine effectiveness against infection varied over time, peaking during the third week with a VE of 64% (95% CI: 62.0%-65.9%) and declining to 29.2% (95% CI: 17.7%-39.1%) by the end of the 10-week follow-up period. Unlike VE against infection, the relative effectiveness of a fourth dose against severe COVID-19 was maintained at high level (>73%) throughout the 9-week follow-up period. Importantly, severe disease was a relatively rare event, occurring in <1% of both fourth dose and third dose only recipients.

- COVID-19 Vaccine Effectiveness against the Omicron BA.2 variant in England (https://www.medrxiv.org/content/10.1101/2022.03.22.22272691v1)
  F Kirseborn et al, MEDRXIV, March 24, 2022

  In this study we use a test-negative case control study design to estimate vaccine effectiveness against symptomatic disease with BA.1 and BA.2 after one or two doses of BNT162b2, ChAdOx1-S or mRNA-1273, and after booster doses of BNT162b2 or mRNA-1273 during a period of co-circulation. Overall, there was no evidence that vaccine effectiveness against symptomatic disease is reduced following infection with the BA.2 sub-lineage as compared to BA.1. Furthermore, similar rates of waning were observed after the second and booster dose for each sub-lineage.

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  > As compared to the Delta variant, neutralizing titers were more markedly decreased against BA.1 (344-fold) than BA.2 (9-fold). We further report 4 breakthrough Omicron infections among the 29 individuals, indicating that antibody treatment did not fully prevent infection. Collectively, BA.1 and BA.2 exhibit noticeable differences in their sensitivity to therapeutic mAbs. Anti-Omicron neutralizing activity of Ronapreve, and to a lesser extent that of Evusheld, is reduced in patients' sera.

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  > A total of 563,465 participants met the eligibility criteria. Of those, 328,597 (58%) received a second-booster dose during the 40-day study period. Death due to Covid-19 occurred in 92 second-booster recipients and in 232 participants who received one booster dose (adjusted hazard ratio 0.22; 95% confidence interval 0.17 to 0.28). This study demonstrates a substantial reduction in Covid-19 mortality by the second-booster in eligible subjects.

- Vulnerability of ß-Thalassemia Heterozygotes to COVID-19: Results from a Cohort Study. (https://pubmed.ncbi.nlm.nih.gov/35330352)
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  An increased mortality risk from COVID-19 was observed for older age, male sex, ß-Thalassemia heterozygosity and respiratory disease. Carriers of ß-Thalassemia were identified as more vulnerable for severe clinical symptomatology, but there was no increased possibility for ICU admission. Readjustment of these findings to consider impacts of variant strains prevailing during the latest viral outbreak among vulnerable patient groups may offer timely relief from the pandemic.
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  > We show that the early stage of the pandemic in Brazil was characterised by the co-circulation of multiple viral lineages, linked to multiple importations predominantly from Europe, and subsequently characterized by large local transmission clusters. As the epidemic progressed under an absence of effective restriction measures, there was a local emergence and onward international spread of Variants of Concern (VOC) and Variants Under Monitoring (VUM), including Gamma (P.1) and Zeta (P.2). In addition, we provide a preliminary genomic overview of the epidemic in Paraguay, showing evidence of importation from Brazil. These data reinforce the usefulness and need for the implementation of widespread genomic surveillance in South America as a toolkit for pandemic monitoring.

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- Relative Effectiveness of Four Doses Compared to Three Dose of the BNT162b2 Vaccine in Israel (https://www.medrxiv.org/content/10.1101/2022.03.24.22272835v1)
  S Gazit et al, MEDRXIV, March 24, 2022

A fourth dose provided considerable additional protection against both SARS-CoV-2 infection and severe disease relative to three doses of the vaccine. However, vaccine effectiveness against infection varied over time, peaking during the third week with a VE of 64% (95% CI: 62.0%-65.9%) and declining to 29.2% (95% CI: 17.7%-39.1%) by the end of the 10-week follow-up period. Unlike VE against infection, the relative effectiveness of a fourth dose against severe COVID-19 was maintained at high level (>73%) throughout the 9-week follow-up period. Importantly, severe disease was a relatively rare event, occurring in <1% of both fourth dose and third dose only recipients.

- COVID-19 Vaccine Effectiveness against the Omicron BA.2 variant in England (https://www.medrxiv.org/content/10.1101/2022.03.22.22272691v1)
  F Kirseborn et al, MEDRXIV, March 24, 2022

  In this study we use a test-negative case control study design to estimate vaccine effectiveness against symptomatic disease with BA.1 and BA.2 after one or two doses of BNT162b2, ChAdOx1-S or mRNA-1273, and after booster doses of BNT162b2 or mRNA-1273 during a period of co-circulation. Overall, there was no evidence that vaccine effectiveness against symptomatic disease is reduced following infection with the BA.2 sub-lineage as compared to BA.1. Furthermore, similar rates of waning were observed after the second and booster dose for each sub-lineage.
- Serum neutralization of SARS-CoV-2 Omicron sublineages BA.1 and BA.2 in patients receiving monoclonal antibodies (https://www.nature.com/articles/s41591-022-01792-5)
  T Bruel et al, Nature Medicine, March 23, 2022

  As compared to the Delta variant, neutralizing titers were more markedly decreased against BA.1 (344-fold) than BA.2 (9-fold). We further report 4 breakthrough Omicron infections among the 29 individuals, indicating that antibody treatment did not fully prevent infection. Collectively, BA.1 and BA.2 exhibit noticeable differences in their sensitivity to therapeutic mAbs. Anti-Omicron neutralizing activity of Ronapreve, and to a lesser extent that of Evusheld, is reduced in patients' sera.
- Structural basis for potent antibody neutralization of SARS-CoV-2 variants including B.1.1.529 (https://www.science.org/doi/10.1126/science.abn8897)
  T Zhou et al, Science, March 24, 2022

  To provide insight into effective neutralization, we determined cryo-EM structures and evaluated receptor-binding domain (RBD) antibodies for their ability to bind and neutralize B.1.1.529. Mutations altered 16% of the B.1.1.529 RBD surface, clustered on a RBD ridge overlapping the ACE2-binding surface and reduced binding of most antibodies. Significant inhibitory activity was retained by select monoclonal antibodies including A19-58.1, B1-182.1, COV2-2196, S2E12, A19-46.1, S309 and LY-CoV1404, which accommodated these changes and neutralized B.1.1.529. We identified combinations of antibodies with synergistic neutralization.
- Inherited Thrombophilias Are Associated With a Higher Risk of COVID-19-Associated Venous Thromboembolism: A Prospective Population-Based Cohort Study.

(https://pubmed.ncbi.nlm.nih.gov/35312380)
Stevens Hannah et al. Circulation 2022 3 (12) 940-942

> The risk of venous thromboembolism (VTE) is markedly increased in patients with COVID-19 (COVID-19 VTE) and is associated with higher COVID-19 mortality. Whether the presence of inherited thrombophilias is associated with a higher risk of COVID-19 VTE remains a key outstanding issue. Using data from the UK Biobank, we report on the association between inherited thrombophilias, COVID-19 VTE, and COVID-19 mortality. Our findings demonstrate for the first time that the thrombophilic SNPs, rs6025 and rs2066865, in addition to the PRS-VTE, are associated with a higher risk of COVID-19 VTE.

- Second Booster Vaccine and Covid-19 Mortality in Adults 60 to 100 Years Old
(https://www.researchsquare.com/article/rs-1478439/v1)
R Arbel et al, Research Square, March 24, 2022

> A total of 563,465 participants met the eligibility criteria. Of those, 328,597 (58%) received a second-booster dose during the 40-day study period. Death due to Covid-19 occurred in 92 second-booster recipients and in 232 participants who received one booster dose (adjusted hazard ratio 0.22; 95% confidence interval 0.17 to 0.28). This study demonstrates a substantial reduction in Covid-19 mortality by the second-booster in eligible subjects.

- Vulnerability of ß-Thalassemia Heterozygotes to COVID-19: Results from a Cohort Study.
(https://pubmed.ncbi.nlm.nih.gov/35330352)
Sotiriou Sotirios et al. Journal of personalized medicine 2022 3 (3)

> An increased mortality risk from COVID-19 was observed for older age, male sex, ß-Thalassemia heterozygosity and respiratory disease. Carriers of ß-Thalassemia were identified as more vulnerable for severe clinical symptomatology, but there was no increased possibility for ICU admission. Readjustment of these findings to consider impacts of variant strains prevailing during the latest viral outbreak among vulnerable patient groups may offer timely relief from the pandemic.

- GSTO1, GSTO2 and ACE2 Polymorphisms Modify Susceptibility to Developing COVID-19.
(https://pubmed.ncbi.nlm.nih.gov/35330457)
Djukic Tatjana et al. Journal of personalized medicine 2022 3 (3)

> The distribution of polymorphisms in ACE2 (rs4646116), GSTO1 (rs4925) and GSTO2 (rs156697) were assessed in 255 COVID-19 patients and 236 matched healthy individuals, emphasizing their individual and haplotype effects on disease development and severity. Polymorphisms were determined by the appropriate qPCR method. The data obtained showed that individuals carrying variant GSTO1*AA and variant GSTO2*GG genotypes exhibit higher odds of COVID-19 development, contrary to ones carrying referent alleles ($p = 0.044$, $p = 0.002$, respectively). These findings are confirmed by haplotype analysis. Carriers of H2 haplotype, comprising GSTO1*A and GSTO2*G variant alleles were at 2-fold increased risk of COVID-19 development ($p = 0.002$).

- COVID-19 Cases and Disease Severity in Pregnancy and Neonatal Positivity Associated With Delta (B.1.617.2) and Omicron (B.1.1.529) Variant Predominance (https://jamanetwork.com/journals/jama/fullarticle/2790609)
  EH Adhikari et al, JAMA< March 24, 2022

  > As in nonpregnant people, Delta and Omicron variant predominance were associated with increased SARS-CoV-2 infections in pregnancy, with the majority occurring in unvaccinated individuals. Delta variant predominance was associated with increased illness severity and Omicron with decreased illness severity after adjusting for prior vaccination. The majority of early neonatal SARS-CoV-2 infections occurred among unvaccinated mothers with nonsevere COVID-19. Long-term risks of early neonatal SARS-CoV-2 infection are unknown, but maternal vaccination may be protective.

- Association of COVID-19 Vaccination in Pregnancy With Adverse Peripartum Outcomes (https://jamanetwork.com/journals/jama/fullarticle/2790607)
  DB Fell et al, JAMA, March 24, 2022

  > Is COVID-19 vaccination during pregnancy associated with adverse peripartum outcomes? In this population-based retrospective cohort study of 97?590 individuals in Ontario, Canada, COVID-19 vaccination during pregnancy, compared with vaccination after pregnancy and with no vaccination, was not significantly associated with increased risk of postpartum hemorrhage, chorioamnionitis, cesarean delivery, admission to neonatal intensive care unit, or low newborn 5-minute Apgar score.

- Association of SARS-CoV-2 Vaccination During Pregnancy With Pregnancy Outcomes (https://jamanetwork.com/journals/jama/fullarticle/2790608)
  MC Magnus et al, JAMA, March 24, 2022

  > Is SARS-CoV-2 vaccination during pregnancy associated with adverse pregnancy outcomes? In this population-based retrospective cohort study that included 157 521 deliveries in Sweden and Norway, SARS-CoV-2 vaccination during pregnancy, compared with no SARS-CoV-2 vaccination during pregnancy, was not significantly associated with risk of preterm birth (adjusted hazard ratio [aHR], 0.98), stillbirth (aHR, 0.86), small for gestational age (adjusted odds ratio [aOR], 0.97), low Apgar score (aOR, 0.97), or neonatal care admission (aOR, 0.97).

- A TMPRSS2 inhibitor acts as a pan-SARS-CoV-2 prophylactic and therapeutic (https://www.nature.com/articles/s41586-022-04661-w)
  T Shapira et al, Nature, March 28, 2022

  > Here, we identify and characterize a small-molecule compound, N-0385, which exhibits low nanomolar potency and a selectivity index of >106 at inhibiting SARS-CoV-2 infection in human lung cells and in donor-derived colonoids7. In Calu-3 cells it inhibits entry of SARS-CoV-2 VOCs, B.1.1.7, B.1.351, P.1 and B.1.617.2. Importantly, in the K18-human ACE2 transgenic mouse model of severe SARS-CoV-2 disease, we found that N-0385 affords a high level of prophylactic and therapeutic benefit following either multiple or even a single administration.

- Levels of SARS-CoV-2 Antibodies Among Fully-Vaccinated Individuals With Delta or Omicron Variant Breakthrough Infections: A Prospective Cohort Study (https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4066425)
  NB Stark et al, SSRN, March 25, 2022

  > We observed a strong association between increasing levels of anti-spike antibodies and reduced risk of breakthrough infections with the Delta but not the Omicron variant. However, despite a high proportion of elderly participants, severe COVID-19 was rare in both Delta and Omicron infections.

- Genomic epidemiology reveals the impact of national and international restrictions measures on the SARS-CoV-2 epidemic in Brazil (https://www.medrxiv.org/content/10.1101/2021.10.07.21264644v2)
  M Giovanetti et al, MEDRXIV, March 28 2022

  > We show that the early stage of the pandemic in Brazil was characterised by the co-circulation of multiple viral lineages, linked to multiple importations predominantly from Europe, and subsequently characterized by large local transmission clusters. As the epidemic progressed under an absence of effective restriction measures, there was a local emergence and onward international spread of Variants of Concern (VOC) and Variants Under Monitoring (VUM), including Gamma (P.1) and Zeta (P.2). In addition, we provide a preliminary genomic overview of the epidemic in Paraguay, showing evidence of importation from Brazil. These data reinforce the usefulness and need for the implementation of widespread genomic surveillance in South America as a toolkit for pandemic monitoring.

- Global landscape of SARS-CoV-2 genomic surveillance and data sharing (https://www.nature.com/articles/s41588-022-01033-y)
  Z Chen et a, Nature Genetics, March 28, 2022

  > We characterize increasing circulation of the Alpha variant in early 2021, subsequently replaced by the Delta variant around May 2021. SARS-CoV-2 genomic surveillance and sequencing availability varied markedly across countries, with 45 countries performing a high level of routine genomic surveillance and 96 countries with a high availability of SARS-CoV-2 sequencing. We also observed a marked heterogeneity of sequencing percentage, sequencing technologies, turnaround time and completeness of released metadata across regions and income groups. A total of 37% of countries with explicit reporting on variants shared less than half of their sequences of variants of concern (VOCs) in public repositories.

- Coronavirus Host Genetics South Africa (COHG-SA) database—a variant database for gene regions associated with SARS-CoV-2 outcomes (https://www.nature.com/articles/s41431-022-01089-8)
  F Barmania et al, EJHG, March 29, 2022

  > The SARS-CoV-2 virus is responsible for the COVID-19 global public health emergency, and the disease it causes is highly variable in its clinical presentation. Clinical phenotypes are heterogeneous both in terms of presentation of symptoms in the host and response to therapy. Several studies and initiatives have been established to analyse and review host genetic epidemiology associated with

COVID-19. Our research group curated these articles into a web-based database using the python application-server framework Django. The database provides a searchable research tool describing current literature surrounding COVID-19 host genetic factors associated with disease outcome.

- Effectiveness of Homologous and Heterologous COVID-19 Booster Doses Following 1 Ad.26.COV2.S (Janssen [Johnson & Johnson]) Vaccine Dose Against COVID-19–Associated Emergency Department and Urgent Care Encounters and Hospitalizations Among Adults — VISION Network, 10 States, December 2021–March 2022 (https://www.cdc.gov/mmwr/volumes/71/wr/mm7113e2.htm)
  K Natarjan et al, MMWR< March 29, 2022

  Little is known about vaccine effectiveness (VE) of different booster strategies following Ad.26.COV2.S (Janssen [Johnson & Johnson]) vaccination, especially during Omicron variant predominance. VE against COVID-19–associated emergency department/urgent care visits was 24% after 1 Jansen dose, 54% after 2 Jansen doses, and 79% after 1 Janssen/1 mRNA dose, compared to 83% after 3 mRNA doses. VE for the same strategies against COVID-19–associated hospitalization was 31%, 67%, 78%, and 90% respectively.

- BNT162b2 Protection against the Omicron Variant in Children and Adolescents. (https://pubmed.ncbi.nlm.nih.gov/35353976)
  Price Ashley M et al. The New England journal of medicine 2022 3

  BNT162b2 vaccination reduced the risk of omicron-associated hospitalization by two thirds among children 5 to 11 years of age. Although two doses provided lower protection against omicron-associated hospitalization than against delta-associated hospitalization among adolescents 12 to 18 years of age, vaccination prevented critical illness caused by either variant.

- Nationwide Effectiveness of First and Second SARS-CoV2 Booster Vaccines during the Delta and Omicron Pandemic Waves in Hungary (HUN-VE 2 Study)
  (https://www.medrxiv.org/content/10.1101/2022.03.27.22273000v1)
  Z Kiss et al, MEDRXIV, March 30, 2022

  The double booster immunized population had a 93% lower risk of Covid-19 related death compared to those with only one booster dose (RR: 0.07; 95% CI. 0.01-0.46). The benefit of the second booster was slightly more pronounced in older age groups.The HUN-VE 2 study demonstrated the significantly lower risk of Covid-19 related mortality associated with the Omicron vs. Delta variant and confirmed the benefit of single and double booster vaccination against Covid-19 related death. Furthermore, the results showed the additional benefit of a second booster dose in terms of SARS-CoV-2 infection and Covid-19 related mortality.

- Exome-wide association study to identify rare variants influencing COVID-19 outcomes: Results from the Host Genetics Initiative (https://www.medrxiv.org/content/10.1101/2022.03.28.22273040v1)
  GB LaPorte et al, MEDRXIV, March 30, 2022

In an analysis of 5,048 severe disease cases and 571,009 controls, we observed that carrying a rare deleterious variant in the SARS-CoV-2 sensor toll-like receptor TLR7 (on chromosome X) was associated with a 5.3-fold increase in severe disease (95% CI: 2.75-10.05, p=5.41x10-7). These results further support TLR7 as a genetic determinant of severe disease and suggest that larger studies on rare variants influencing COVID-19 outcomes could provide additional insights.

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