THE BEST OF THE WEEK (21 nov – 27 nov 2022)

Freja Cordelia Møller Kirsebom et al.

Effectiveness of the COVID-19 vaccines against hospitalisation with Omicron sub-lineages BA.4 and BA.5 in England

Science Direct, November 2022; doi.org/10.1016/j.lanepe.2022.100537

The Omicron sub-lineages BA.4 and BA.5, identified in South Africa in early 2022,1 were first detected in England in April 2022.2 A case surge followed despite England having recently experienced waves with BA.1 and BA.2. BA.4 and BA.5 have identical spike proteins most similar to that of BA.2 but with additional mutations including the 69–70 deletion, L452R, F486V and wild-type amino acid at position Q493.1 Neutralisation assays have found BA.4 and BA.5 display increased evasion of antibodies from plasma of vaccinated or BA.1 infected individuals, as compared to BA.2.3, 4, 5 Recent data from Denmark and Portugal have found that the odds of being vaccinated did not differ amongst BA.5 and BA.2 cases.6,7 The Portuguese study did find lower VE against hospitalisation for BA.5 using a cohort study design.6 The UK COVID-19 vaccination program has been in place since December 2020 with primary courses of two doses of BNT162b2 (Pfizer-BioNTech), ChAdOx1-S (AstraZeneca) or mRNA-1273 (Moderna). Third doses with either BNT162b2 or a half dose (50 μg) of mRNA-1273 were offered to all adults by December 2021. Fourth doses were offered to those at risk and those aged 75 years and older from March 2022. We used a test-negative case–control (TNCC) study design to investigate VE against hospitalisation for BA.4, BA.5 and BA.2 during a period of co-circulation, as previously described.8, 9, 10 The PCR test result was included as the dependent variable and cases being those tested positive for either BA.2, BA.4, BA.5, or BA.4 and BA.5, and controls being those tested negative. Vaccination status was included as an independent variable and effectiveness was defined as 1-odds of vaccination in cases/odds of vaccination in controls. For BA.2, VE following a third or fourth dose was comparable (Supplementary Table S2). Therefore, incremental VE was estimated in those vaccinated with either a third or fourth dose as compared to individuals with waned immunity who had received their second dose at least 25 weeks prior (full details in Supplementary Appendix). Between 18 April and 28 August 2022 there were 48,623 eligible tests from individuals hospitalised for at least 2 days and with a respiratory code in the primary diagnosis field. Of these, 36,474 were negative (controls), 3136 were BA.2, 463 were BA.4, 2432 were BA.5 and 6118 were either BA.4 or BA.5 cases (Supplementary Table S3). There was no evidence of reduced VE against hospitalisation for BA.4 or BA.5 as compared to BA.2 (Fig. 1, Supplementary Tables S4 and S5). In those who had received their third or fourth dose 2–14 weeks ago, the incremental VE as compared to those who were 25 or more weeks post their second dose was 60.9% (95% C.I.; 42.2–73.5%) and 62.1% (95% C.I.; 54.4–68.4%) for BA.4 and BA.5, respectively, and 50.1% (95% C.I.; 40.7–58.0%) for BA.2 (Supplementary Table S4). Incremental VE waned to 16.2% (95% C.I.; −18.7 to 40.9%), 23.8% (95% C.I.; 9.8–35.6%) and 9.0% (95% C.I.; −6.8 to 22.4%) for BA.4, BA.5 and BA.2 at 25 or more weeks. To investigate VE by manufacturer, we stratified by final (third or fourth) dose manufacturer (BNT162b2 or mRNA-1273). BA.4 and BA.5 cases were combined for precision. There was no difference in VE against hospitalisation for BA.4/5 as compared to BA.2 (Fig. 1b and c, Supplementary Table S5). VE against hospitalisation with BA.4/5 or BA.2 was slightly higher for mRNA-1273 than BNT162b2 at all time-points investigated, but confidence intervals overlapped. Incremental VE against hospitalisation with

BA.4/5 was 63.2% (95% C.I.; 58.4–67.5%) and 53.1% (95% C.I.; 46.7–58.8%) for mRNA-1273 and BNT162b2, respectively, at 2–14 weeks after receiving a third or fourth dose (Fig. 1b and c, Supplementary Table S5). This decreased to a VE of 40.2% (95% C.I.; 30.3–48.7%) and 23.7% (95% C.I.; 15.0–31.4%) for mRNA-1273 and BNT162b2, respectively, at 15–24 weeks. These data provide reassuring evidence of the protection conferred by the current vaccines against severe disease with BA.4 and BA.5; we found no difference in VE as compared to BA.2 and BNT162b2 and mRNA-1273 boosters provided similarly high levels of protection. This contradicts pre-printed data from a cohort study in Portugal which found VE against severe outcomes was lower for BA.5.6 This may be due to the small size of the Portuguese study, methodological differences, or differences in classifying hospitalised cases. Here, we use a strict definition as we have previously found broader definitions give lower estimates which likely reflect VE against symptomatic disease.10 Risk factor status and previous infection will also impact VE; these analyses include adjustment by most recent previous variant and by the risk factor groups offered early vaccination which the Portuguese study did not. Differences in testing policies between countries will also impact local ability to adjust for factors such as previous infection.

Bonenfant G et al.

Surveillance and Correlation of Severe Acute Respiratory Syndrome Coronavirus 2 Viral RNA, Antigen, Virus Isolation, and Self-Reported Symptoms in a Longitudinal Study With Daily Sampling

CID, April 2022;doi.org/10.1093/cid/ciac282

Abstract

The novel coronavirus pandemic incited unprecedented demand for assays that detect viral nucleic acids, viral proteins, and corresponding antibodies. The 320 molecular diagnostics in receipt of US Food and Drug Administration emergency use authorization mainly focus on viral detection; however, no currently approved test can be used to infer infectiousness, that is, the presence of replicable virus. As the number of tests conducted increased, persistent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA positivity by reverse-transcription polymerase chain reaction (RT-PCR) in some individuals led to concerns over quarantine guidelines. To this end, we attempted to design an assay that reduces the frequency of positive test results from individuals who do not shed culturable virus. We describe multiplex quantitative RT-PCR assays that detect genomic RNA (gRNA) and subgenomic RNA (sgRNA) species of SARS-CoV-2, including spike, nucleocapsid, membrane, envelope, and ORF8. Viral RNA abundances calculated from these assays were compared with antigen presence, self-reported symptoms, and culture outcome (virus isolation) using samples from a 14-day longitudinal household transmission study. By characterizing the clinical and molecular dynamics of infection, we show that sgRNA detection has higher predictive value for culture outcome compared to detection of gRNA alone. Our findings suggest that sgRNA presence correlates with active infection and may help identify individuals shedding culturable virus.

Brest P et al

Host genetic variability and determinants of severe COVID-19

CELL, November 2022; doi.org/10.1016/j.tig.2022.10.003

Abstract

Since the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak, convergent studies have provided evidence that host genetic background may contribute to the development of severe coronavirus disease (COVID-19). Here, we summarize how some genetic variations, such as in SARS-CoV-2 receptor angiotensin-converting enzyme 2 or interferon signaling pathway, may help to understand why some individuals can develop severe COVID-19 persistence has decreased.

Xuping Xie et al.

Neutralization of SARS-CoV-2 Omicron sublineages by 4 doses of the original mRNA vaccine

CELL, November 2022; doi.org/10.1016/j.celrep.2022.111729

Abstract

Since the initial emergence of SARS-CoV-2 Omicron BA.1, several Omicron sublineages have emerged, leading to BA.5 as the current dominant sublineage. Here we report the neutralization of different Omicron sublineages by human sera collected from individuals who had distinct mRNA vaccination and/or BA.1 infection. Four-dose-vaccine sera neutralize the original USA-WA1/2020, Omicron BA.1, BA.2, BA.2.12.1, BA.3, and BA.4/5 viruses with geometric mean titers (GMTs) of 1554, 357, 236, 236, 165, and 95, respectively; 2-dose-vaccine-plus-BA.1-infection sera exhibit GMTs of 2114, 1705, 730, 961, 813, and 274, respectively; and 3-dose-vaccine-plus-BA.1-infection sera show GMTs of 2962, 2038, 983, 1190, 1019, and 297, respectively. Thus, 4-dose-vaccine elicits the lowest neutralization against BA.5; 2-dose-vaccine-plus-BA.1-infection elicits significantly higher GMTs against Omicron sublineages than 4-dose-vaccine; and 3-dose-vaccine-plus-BA.1-infection elicits slightly higher GMTs (statistically insignificant) than the 2-dose-vaccine-plus-BA.1-infection. Finally, the BA.2.75 is more susceptible than BA.5 to 4-dose-vaccine-elicited neutralization and 3-dosevaccine-plus-BA.1-infection-elicited neutralization.

Hyung-Joon Kwon et al.

Enhanced virulence and waning vaccine-elicited antibodies account for breakthrough infections caused by SARS-CoV-2 Delta and beyond

CELL, November 2022; doi.org/10.1016/j.isci.2022.105507

Abstract

Summary Here we interrogate the factors responsible for SARS-CoV-2 breakthrough infections in a K18-hACE2 transgenic mouse model. We show that Delta and the closely related Kappa variant cause viral pneumonia and severe lung lesions in K18-hACE2 mice. Human COVID-19 mRNA post-vaccination sera after the 2nd dose are significantly less efficient in neutralizing Delta/Kappa than early 614G virus in vitro and in vivo. By 5 months post-vaccination, ≥50% of donors lack detectable neutralizing antibodies against Delta and Kappa and all mice receiving 5-month post-vaccination sera die after the lethal challenges. Although a 3rd vaccine dose can boost antibody neutralization against Delta in vitro and in vivo, the mean log neutralization titers against the latest Omicron subvariants are 1/3- 1/2 of those against the original 614D virus. Our results suggest that enhanced virulence, greater immune evasion and waning of vaccine-elicited protection account for SARS-CoV-2 variants caused breakthrough infections.