

## SARS-COV-2 VİRÜSÜNÜN YAPISI VE VİROLOJİK ÖZELLİKLERİ

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### GİRİŞ

Koronavirüsler, kuş, yabani ya da evcil bazı memeliler ve insanlar dahil olmak üzere çok çeşitli konakçıları enfekte edebilen zarflı, tek sarmallı RNA virüsleridir. Genomik organizasyon ve filogenetik ilişki temelinde, koronavirüs ailesi dört cinsten oluşmaktadır: Alfakoronavirüs ( $\alpha$ CoV), Betakoronavirüs ( $\beta$ CoV), Gamakoronavirüs ( $\gamma$ CoV) ve Deltakoronavirüs ( $\delta$ CoV)[1]. Koronavirüslerin evrimsel analizi,  $\alpha$ CoV ve  $\beta$ CoV'nin yarasa ve kemirgenlerden,  $\gamma$ CoV ve  $\delta$ CoV'nin ise kuş türlerinden kaynaklandığını ortaya çıkarmıştır[2]. Koronavirüsler, hızlı mutasyona uğrama, doku tropizmini değiştirme, tür bariyerini aşma ve farklı epidemiyolojik durumlara uyum sağlama yetenekleriyle bilinir[3]. 1960'lardan beri altı insan koronavirüsü rapor edilmiştir; bunlardan dördü (OC43, 229E, NL63 ve HKU1), soğuk algınlığı ve gastrointestinal sistem enfeksiyonu benzeri semptomlarla giden hafif hastalığa neden olurlar. Diğer ikisi, şiddetli akut solunum

sendromu koronavirüsü (SARS-CoV) ve Orta Doğu solunum sendromu koronavirüsü (MERS-CoV), zoonotik ortaya çıkmaları ve tür bariyerini geçerek insanlarda yüksek patojenite ve ölüm oranlarına neden olmaları nedeniyle önemli halk sağlığı problemlerine neden olmuştur. SARS-CoV ve MERS-CoV'ların ana konakçıdan (yarasalar) sırasıyla misk kedilerine veya tek hörgüçlü develere, ardından son olarak insanlara[4-6] aktarıldığı bildirilmiştir. Hem SARS- hem de MERS-CoV'lar yüksek derecede patojenik olup %9.6 ve %34.3 fatalite oranlarıyla sırasıyla 774 ve 866 kişinin ölümüne yol açmışlardır[7,8].

Aralık 2019'da Wuhan şehrinde kümelenen pnömoninin nedensel etkeninin yapılan çalışmalar neticesinde insanda hastalık yapan yedinci bir koronavirüs olduğu saptanmıştır. Bu virüs önce geçici olarak 2019 yeni koronavirüs (2019-nCoV) olarak adlandırılmış daha sonra Uluslararası Virüs Taksonomi Komitesi tarafından şiddetli akut solunum sendromu koronavirüs-2 (SARS-CoV-2)

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laş ve çok nadiren vertikal bulaşın da örnekleri vardır.

- Virüs sıcaklığın artmasıyla daha hızlı inaktive olur. UVC ve kısmen UVB de belli bir süre sonra virüsü inaktive eder.
- Virüs bir RNA virüsü olduğu için sık mutasyona uğrar ancak bu mutasyonun fenotipe yansiyıp yansımayacağı değişkendir.
- Virüsün birçok T hücre ve B hücre epitopu olduğu için meydana gelen mutasyonun mevcut aşuların tamamen etkisiz olmasına yol açması beklenmemektedir.

## KAYNAKÇA

1. Adachi S, Koma T, Nomaguchi M, Adachi A. Commentary: origin and evolution of pathogenic coronaviruses. *Frontiers in immunology*. 2020; 11, 811. doi:10.1038/s41579-018-0118-9
2. Ge XY, Yang WH, Zhou JH, Li B, Zhang W, Shi ZL et al. Detection of alpha-and betacoronaviruses in rodents from Yunnan, China. *Virology journal*. 2017; 14(1), 1-11. doi:10.1186/s12985-017-0766-9
3. Helmy YA, Fawzy M, Elswad A, Sobieh A, Kenney SP, Shehata AA. The COVID-19 pandemic: a comprehensive review of taxonomy, genetics, epidemiology, diagnosis, treatment, and control. *Journal of clinical medicine*. 2020; 9(4), 1225.
4. Guan Y, Zheng B, He Y, Liu X, Zhuang Z, Cheung C, et al. Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. *Science*. 2003; 302, 276–278.
5. Drosten C, Meyer B, Müller M. Supplement to: Transmission of MERS-coronavirus in household contacts. *N. Engl. J. Med*. 2014; 371, 1–10.
6. Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. *Nat. Rev. Microbiol*. 2019; 17, 181–192.
7. WHO (2015). Summary of Probable SARS Cases with Onset of Illness from 1 November 2002 to 31 July 2003. 20/01/2021 tarihinde [https://www.who.int/csr/sars/country/table2004\\_04\\_21/en/adresinden-ulaşilmiştir](https://www.who.int/csr/sars/country/table2004_04_21/en/adresinden-ulaşilmiştir).
8. WHO (2020). MERS Situation Update, January 2020. 20/01/2021 tarihinde <http://www.emro.who.int/pandemic-epidemic-diseases/mers-cov/mers-situation-update-january-2020.html> adresinden ulaşılmıştır.
9. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020; 395, 497–506.
10. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020; 579, 270–273.
11. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: A study of a family cluster. *Lancet*. 2020; 395, 514–523.
12. Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF. The proximal origin of SARS-CoV-2. *Nat. Med*. 2020; 26(4), 450-452. doi:10.1038/s41591-020-0820-9.
13. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J. A novel coronavirus from patients with pneumonia in China, 2019. *New England journal of medicine*. 2020.
14. Masters, P. S. & Perlman, S. in *Fields Virology* 6th edn. Knipe, D. M. & Howley, P. M (Eds.), 826–858 (Elsevier, 2013).
15. Neuman BW, Adair BD, Yoshioka C, Quispe JD, Orca G, Kuhn P, et al. Supramolecular architecture of severe acute respiratory syndrome coronavirus revealed by electron cryomicroscopy. *Journal of virology*. 2006; 80(16), 7918-7928.
16. Chan JFW, Kok KH, Zhu Z, Chu H, To KKW, Yuan S et al. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerging microbes & infections*. 2020; 9(1), 221-236.
17. Kumar S. Drug and vaccine design against Novel Coronavirus (2019- nCoV) spike protein through Computational approach. 2020;1e16.
18. Glowacka I, Bertram S, Müller MA, Allen P, Soilieux E, Pfefferle S, et al. Evidence that TMPRSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response. *Journal of virology*. 2011; 85(9), 4122-4134.
19. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science*. 2020; 367(6483), 1260-1263.
20. Jaimes JA, Andre NM, Chappie JS, Millet JK, Whittaker GR. Phylogenetic analysis and structural modeling of SARS-CoV-2 spike protein reveals an evolutionary distinct and proteolytically sensitive activation loop. *Journal of molecular biology*. 2020; 432(10), 3309-3325.
21. Cai Y, Zhang J, Xiao T, Peng H, Sterling SM, Walsh RM, et al. Distinct conformational states of SARS-CoV-2 spike protein. *Science* 2020; 369(6511), 1586-1592.

22. Huang Q, Yu L, Petros AM, Gunasekera A, Liu Z, Xu N, et al. Structure of the N-terminal RNA-binding domain of the SARS CoV nucleocapsid protein. *Biochemistry*. 2004; 43(20), 6059-6063.
23. Gralinski LE, Menachery VD. Return of the coronavirus: 2019- nCoV. *Viruses*. 2020; 12(2), 135.
24. Yan X, Hao Q, Mu Y, Timani KA, Ye L, Zhu Y, et al. Nucleocapsid protein of SARS-CoV activates the expression of cyclooxygenase-2 by binding directly to regulatory elements for nuclear factor-kappa B and CCAAT/enhancer binding protein. *The international journal of biochemistry & cell biology*. 2006; 38(8), 1417-1428.
25. Zeng Y, Ye L, Zhu S, Zheng H, Zhao P, Cai W, et al. The nucleocapsid protein of SARS-associated coronavirus inhibits B23 phosphorylation. *Biochemical and biophysical research communications*. 2008; 369(2), 287-291.
26. Wang Q, Li C, Zhang Q, Wang T, Li J, Guan W, et al. Interactions of SARS coronavirus nucleocapsid protein with the host cell proteasome subunit p42. *Virology journal*. 2010; 7(1), 1-8.
27. Lu X, Pan JA, Tao J, Guo D. SARS-CoV nucleocapsid protein antagonizes IFN- $\beta$  response by targeting initial step of IFN- $\beta$  induction pathway, and its C-terminal region is critical for the antagonism. *Virus genes*. 2011; 42(1), 37-45.
28. Liu DX, Yuan Q, Liao Y. Coronavirus envelope protein: A small membrane protein with multiple functions. *Cell Mol Life Sci*. 2007; 64: 2043-2048
29. Schoeman D, Fielding BC. Coronavirus envelope protein: Current knowledge. *Virol J*. 2019;16:1-22.
30. J Alsaadi EA, Jones IM. Membrane binding proteins of coronaviruses. *Future Virol*. 2019;14:275e286.
31. Arndt AL, Larson BJ, Hogue BG. A Conserved Domain in the Coronavirus Membrane Protein Tail Is Important for Virus Assembly. *J Virol*. 2010;84, 11418-11428.
32. Fang X, Gao J, Zheng H, Li B, Kong L, Zhang Y, et al. The membrane protein of SARS-CoV suppresses NF- $\kappa$ B activation. *Journal of medical virology*. 2007; 79(10), 1431-1439.
33. Wang Y, Liu L. The membrane protein of severe acute respiratory syndrome coronavirus functions as a novel cytosolic pathogen-associated molecular pattern to promote beta interferon induction via a Toll-like-receptor-related TRAF3-independent mechanism. *MBio*. 2016; 7(1).
34. Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. In Maier HJ, Bickerton E, Britton P (eds.). *Coronaviruses. Methods in Molecular Biology*. 1282. Springer. 2015; 1-23. doi:10.1007/978-1-4939-2438-7\_1.
35. Discngine (2020) SARS-CoV-2 - part 2 - From the viral genome to protein structures. 20/01/2021 tarihinde <https://www.discngine.com/blog/2020/3/27/sars-cov-2-2-from-the-viral-genome-towards-protein-structures> adresinden ulaşılmıştır.
36. Belouzard S, Chu VC, Whittaker GR. Activation of the SARS coronavirus spike protein via sequential proteolytic cleavage at two distinct sites. *Proc Natl Acad Sci*. 2009; 106(14), 5871-5876. doi: 10.1073/pnas.08095 24106.
37. Bosch BJ, van der Zee R, de Haan CA, et al. The coronavirus spike protein is a class I virus fusion protein: structural and functional characterization of the fusion core complex. *J Virol*. 2003; 77:8801-8811.
38. Ou T, Mou H, Zhang L, Ojha A, Choe H, Farzan M. Hydroxychloroquine-mediated inhibition of SARS-CoV-2 entry is attenuated by TMPRSS2. *PLoS pathogens*. 2021;17(1), e1009212.
39. Cevik M, Kuppalli K, Kindrachuk J, Peiris M. Virology, transmission, and pathogenesis of SARS-CoV-2. *BMJ*. 2020; 371.
40. Baranov PV, Henderson CM, Anderson CB et al. Programmed ribosomal frameshifting in decoding the SARS-CoV genome. *Virology*. 2005; 332:498-510. doi: 10.1016/j. virol.2004.11.038.
41. Brierley I, Digard P, Inglis SC (1989) Characterization of an efficient coronavirus ribosomal frameshifting signal: requirement for an RNA pseudoknot. *Cell* 57:537-547.
42. Ziebuhr J, Snijder EJ, Gorbalenya AE. Virus-encoded proteinases and proteolytic processing in the Nidovirales. *J Gen Virol*. 2000; 81:853-879.
43. Mielech AM, Chen Y, Mesecar AD, Baker SC. Nidovirus papain-like proteases: multifunctional enzymes with protease, deubiquitinating and delSgylating activities. *Virus research*. 2014; 194, 184-190.
44. Snijder EJ, Bredenbeek PJ, Dobbe JC, Thiel V, Ziebuhr J, Poon LL, et al. Unique and conserved features of genome and proteome of SARS-coronavirus, an early split-off from the coronavirus group 2 lineage. *Journal of molecular biology*. 2003; 331(5), 991-1004.
45. Sethna PB, Hofmann MA, Brian DA. Minus-strand copies of replicating coronavirus mRNAs contain antileaders. *J Virol*. 1991; 65:320-325.
46. Sola I, Mateos-Gomez PA, Almazan F, Zuniga S, Enjuanes L. RNA-RNA and RNA-protein interactions in coronavirus replication and transcription. *RNA biology*. 2011; 8(2), 237-248.
47. Subissi L, Imbert I, Ferron F, Collet A, Coutard B, Decroly E, et al. SARS-CoV ORF1b-encoded nonstructural proteins 12-16: replicative enzymes as antiviral targets. *Antiviral research*. 2014; 101, 122-130.
48. Denison MR, Graham RL, Donaldson EF, Eckerle LD, Baric RS. Coronaviruses: an RNA proofreading

- machine regulates replication fidelity and diversity. *RNA Biol.* 2011; 8:270–279.
49. Krijnse-Locker J, Ericsson M, Rottier PJ, Griffiths G. Characterization of the budding compartment of mouse hepatitis virus: evidence that transport from the RER to the Golgi complex requires only one vesicular transport step. *The Journal of cell biology.* 1994; 124(1), 55-70.
  50. Siu YL, Teoh KT, Lo J, Chan CM, Kien F, Escriou N, et al. The M, E, and N structural proteins of the severe acute respiratory syndrome coronavirus are required for efficient assembly, trafficking, and release of virus-like particles. *Journal of virology.* 2008; 82(22), 11318-11330. doi: 10.1128/JVI.01052-08
  51. Boscarino JA, Logan HL, Lacny JJ, Gallagher TM. Envelope protein palmitoylations are crucial for murine coronavirus assembly. *Journal of virology.* 2008; 82(6), 2989-2999. doi: 10.1128/JVI.01906-07
  52. Ye Y, Hogue BG. Role of the coronavirus E viroporin protein transmembrane domain in virus assembly. *J Virol.* 2007; 81:3597–3607. doi: 10.1128/JVI.01472-06
  53. WHO (2014). Infection prevention and control of epidemic-and pandemic prone acute respiratory infections in healthcare – WHO guidelines. 20/01/2021 tarihinde [http://www.who.int/csr/bioriskreduction/infection\\_control/publication/en/adresinden ulařılmıřtır](http://www.who.int/csr/bioriskreduction/infection_control/publication/en/adresinden ulařılmıřtır).
  54. Thomas RJ. Particle size and pathogenicity in the respiratory tract. *Virulence.* 2013; 4:847–858.
  55. Wonderlich ER, Swan ZD, Bissel SJ, Hartman AL, Carney JP, O'Malley KJ, et al. Widespread virus replication in alveoli drives acute respiratory distress syndrome in aerosolized H5N1 influenza infection of macaques. *The Journal of Immunology.* 2017; 198(4), 1616-1626.
  56. Liu L, Wei J, Li Y, Ooi A. Evaporation and dispersion of respiratory droplets from coughing. *Indoor Air.* 2017; 27:179–90. doi: 10.1111/ina.12297
  57. Cevik M, Tate M, Lloyd O, Maraolo AE, Schafers J, Ho A. SARS-CoV-2, SARS-CoV-1 and MERS-CoV viral load dynamics, duration of viral shedding and infectiousness: a living systematic review and meta-analysis. *medRxiv.* 2020; doi: 10.1101/2020.07.25.20162107
  58. Cai J, Sun W, Huang J, Gamber M, Wu J, He G. Indirect virus transmission in cluster of COVID-19 cases, Wenzhou, China, 2020. *Emerg Infect Dis.* 2020; 26:1343-1345. doi:10.3201/eid2606.200412.
  59. Lessells, R., Moosa, Y., & De Oliveira, T. (2020). Report into a nosocomial outbreak of coronavirus disease 2019 (COVID-19) at Netcare St. Augustine's Hospital.
  60. Van Kampen JJ, van de Vijver DA, Fraaij PL, Hagmans BL, Lamers MM, Okba N, et al. Shedding of infectious virus in hospitalized patients with coronavirus disease-2019 (COVID-19): duration and key determinants. *MedRxiv.* 2020; doi:10.1101/2020.06.08.20125310.
  61. Cheng HY, Jian SW, Liu DP, Ng TC, Huang WT, Lin HH. Contact tracing assessment of COVID-19 transmission dynamics in Taiwan and risk at different exposure periods before and after symptom onset. *JAMA internal medicine.* 2020; 180(9), 1156-1163. doi:10.1001/jamainternmed.2020.2020.
  62. Shi J, Wen Z, Zhong G, Yang H, Wang C, Huang B, et al. Susceptibility of ferrets, cats, dogs, and other domesticated animals to SARS–coronavirus 2. *Science.* 2020; 368(6494), 1016-1020. doi:10.1126/science.abb7015 .
  63. Richard M, Kok A, de Meulder D, Bestebroer TM, Lamers MM, Okba NM, et al. SARS-CoV-2 is transmitted via contact and via the air between ferrets. *Nature communications.* 2020; 11(1), 1-6. doi:10.1038/s41467-020-17367-2.
  64. Garigliany M, Van Laere AS, Clercx C, Giet D, Escriou N, Huon C, et al. SARS-CoV-2 natural transmission from human to cat, Belgium, March 2020. *Emerg Infect Dis.* 2020;26. doi:10.3201/eid2612.202223.
  65. Halfmann PJ, Hatta M, Chiba S, Maemura T, Fan S, Takeda M, et al. Transmission of SARS-CoV-2 in domestic cats. *New England Journal of Medicine.* 2020; 383(6), 592-594. doi:10.1056/NEJMc2013400.
  66. Oreshkova N, Molenaar RJ, Vreman S, Harders F, Munnink BBO, Hakze-van Der Honing RW, et al. SARS-CoV-2 infection in farmed minks, the Netherlands, April and May 2020. *Eurosurveillance.* 2020; 25(23), 2001005. doi:10.2807/1560-7917.ES.2020.25.23.2001005.
  67. Munnink BBO, Sikkema RS, Nieuwenhuijse DF, Molenaar RJ, Munger E, Molenkamp R, et al. Jumping back and forth: anthroozoonotic and zoonotic transmission of SARS-CoV-2 on mink farms. *bioRxiv.* 2020; doi:10.1101/2020.09.01.277152.
  68. Zeng L, Xia S, Yuan W, Yan K, Xiao F, Shao J, et al. Neonatal early-onset infection with SARS-CoV-2 in 33 neonates born to mothers with COVID-19 in Wuhan, China. *JAMA pediatrics.* 2020; 174(7), 722-725. doi:10.1001/jamapediatrics.2020.0878.
  69. Alzamora MC, Paredes T, Caceres D, Webb CM, Valdez LM, La Rosa M. Severe COVID-19 during pregnancy and possible vertical transmission. *American journal of perinatology.* 2020; 37(8), 861. doi:10.1055/s-0040-1710050.
  70. Patanè L, Morotti D, Giunta MR, Sigismondi C, Piccoli MG, Frigerio L, et al. Vertical transmission of coronavirus disease 2019: severe acute respi-

- ratory syndrome coronavirus 2 RNA on the fetal side of the placenta in pregnancies with coronavirus disease 2019—positive mothers and neonates at birth. *American journal of obstetrics & gynecology MFM*. 2020; 2(3), 100145. doi: 10.1016/j.ajogmf.2020.100145.
71. Vivanti AJ, Vuloup-Fellous C, Prevot S, Zupan V, Suffee C, Do Cao J, et al. Transplacental transmission of SARS-CoV-2 infection. *Nature communications*. 2020; 11(1), 1-7. doi:10.1038/s41467-020-17436-6.
  72. Alamar I, Abu-Arja MH, Heyman T, Roberts DJ, Desai N, Narula P, et al. A possible case of vertical transmission of SARS-CoV-2 in a newborn with positive placental in situ hybridization of SARS-CoV-2 RNA. *Journal of the Pediatric Infectious Diseases Society*. 2020; doi:10.1093/jpids/piaa109.
  73. Groß R, Conzelmann C, Müller JA, Stenger S, Steinhart K, Kirchhoff F, et al. Detection of SARS-CoV-2 in human breastmilk. *The Lancet*. 2020; 395(10239), 1757-1758. doi:10.1016/S0140-6736(20)31181-8.
  74. Chambers C, Krogstad P, Bertrand K, Contreras D, Tobin NH, Bode L, et al. Evaluation for SARS-CoV-2 in breast milk from 18 infected women. *Jama*. 2020; 324(13), 1347-1348. doi:10.1001/jama.2020.15580.
  75. Deng W, Bao L, Gao H, Xiang Z, Qu Y, Song Z, et al. Ocular conjunctival inoculation of SARS-CoV-2 can cause mild COVID-19 in rhesus macaques. *Nature communications*. 2020; 11(1), 1-7. doi:10.1101/2020.03.13.990036.
  76. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARS-CoV-2 in different types of clinical specimens. *Jama*. 2020; 323(18), 1843-1844. doi:10.1001/jama.2020.3786.
  77. Kim JM, Kim HM, Lee EJ, Jo HJ, Yoon Y, Lee NJ, et al. Detection and isolation of SARS-CoV-2 in serum, urine, and stool specimens of COVID-19 patients from the Republic of Korea. *Osong public health and research perspectives*. 2020; 11(3), 112. doi:10.24171/j.phrp.2020.11.3.02.
  78. Parasa S, Desai M, Chandrasekar VT, Patel HK, Kenned KF, Roesch T, et al. Prevalence of gastrointestinal symptoms and fecal viral shedding in patients with coronavirus disease 2019: a systematic review and meta-analysis. *JAMA network open*. 2020; 3(6), e2011335-e2011335. doi:10.1001/jamanetworkopen.2020.11335.
  79. van Doorn AS, Meijer B, Frampton CM, Barclay ML, de Boer NK. Systematic review with meta-analysis: SARS-CoV-2 stool testing and the potential for faecal-oral transmission. *Alimentary pharmacology & therapeutics*. 2020; 52(8), 1276-1288. doi:10.1111/apt.16036.
  80. Patel J. Viability of SARS-CoV-2 in faecal bio-aerosols [Letter]. *Colorectal Dis*. 2020. doi:10.1111/codi.15181.
  81. Hogan CA, Stevens BA, Sahoo MK, Huang C, Garamani N, Gombar S, et al. High frequency of SARS-CoV-2 RNAemia and association with severe disease. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*. 2020; doi:10.1101/2020.04.26.20080101.
  82. Fajnzylber J, Regan J, Coxen K, Corry H, Wong C, Rosenthal A, et al. SARS-CoV-2 viral load is associated with increased disease severity and mortality. *Nature communications*. 2020; 11(1), 1-9. doi:10.1101/2020.07.15.20131789.
  83. Le Chang LZ, Gong H, Wang L, Wang L. Severe acute respiratory syndrome coronavirus 2 RNA detected in blood donations. *Emerg Infect Dis*. 2020; 26(7), 1631. doi:10.3201/eid2607.200839.
  84. Chin AW, Chu JT, Perera MR, Hui KP, Yen HL, Chan MC, et al. Stability of SARS-CoV-2 in different environmental conditions. *The Lancet Microbe*. 2020. [https://doi.org/10.1016/S2666-5247\(20\)30003-3](https://doi.org/10.1016/S2666-5247(20)30003-3).
  85. Morris DH, Yinda KC, Gamble A, Rossine FW, Huang Q, Bushmaker T, et al. The effect of temperature and humidity on the stability of SARS-CoV-2 and other enveloped viruses. *bioRxiv*. 2020. doi: 10.1101/2020.10.16.341883.
  86. Ratnesar-Shumate S, Williams G, Green B, Krause M, Holland B, Wood S, et al. Simulated Sunlight Rapidly Inactivates SARS-CoV-2 on Surfaces. *The Journal of infectious diseases* 2020; 222(2), 214–222. doi: 10.1093/infdis/jiaa274.
  87. Seyer A, Sanlidag T. Solar ultraviolet radiation sensitivity of SARS-CoV-2. *Lancet Microbe*. 2020; 1, 8–9.
  88. Bulfone TC, Malekinejad M, Rutherford GW, Razani N. Outdoor Transmission of SARS-CoV-2 and Other Respiratory Viruses, a Systematic Review. *The Journal of infectious diseases*. 2020.
  89. Luring AS, Hodcroft EB. Genetic Variants of SARS-CoV-2—What Do They Mean? *JAMA*. 2021. doi:10.1001/jama.2020.27124.
  90. Li W, Li L, Sun T, He Y, Liu G, Xiao Z, et al. Spike protein-based epitopes predicted against SARS-CoV-2 through literature mining. *Med Nov Technol Device*. 2020;100048. doi: 10.1016/j.medntd.2020.100048.
  91. Weisblum Y, Schmidt F, Zhang F, DaSilva J, Poston D, Lorenzi JC, et al. Escape from neutralizing antibodies by SARS-CoV-2 spike protein variants. *Elife*. 2020; 9, e61312.
  92. Xie X, Liu Y, Liu J, Zhang X, Zou J, Fontes-Garfias CR, et al. Neutralization of SARS-CoV-2 spike 69/70 deletion, E484K, and N501Y variants by BNT162b2 vaccine-elicited sera. *Nat Med* (2021). Doi:10.1038/s41591-021-01270-4.