LISTA DE REFERÊNCIAS BIBLIOGRÁFICAS E RESUMOS– COVID -19

Atualizado em: 4 de março de 2022

Título	Defensin 5 for prevention of SARS-CoV-2 invasion and Covid-19 disease
Autor(es)	Yaron Niv
Resumo	Corona virus disease 2019 (Covid-19), a pandemia emerged recently, caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). The receptor for corona virus and influenza A is the mucosal cell membrane protein angiotensin converting enzyme 2 (ACE2), which is abundant on the membrane of alveolar cells and enterocytes. Viral spike protein 1 (S1) is the ligand, with an affinity of 14.7 nM to the receptor. The main port of entry for the virus is the upper respiratory tract, and the diagnosis is usually by PCR of the viral RNA with nasal and pharyngeal swab test. Human defensin 5 (HDEF5) is a protein encoded by the DEFA gene, secreted by Paneth cells in the small intestine and by granules of neutrophils. It has an affinity of 39.3 nM to ACE2, much higher than that of the corona S1. HDEF5 may also attach to glycosylated Corona S1 protein, make its efficiency even better. The issues to be investigated are the affinity of HDEF5 to S1 protein, the ability of recombinant HDEF5 function in attaching both ACE2 and S1, and the feasibility to perform aerosol spray of this protein. In addition, safety and efficiency should be studied in phases I, II and II clinical protocols. Thus, an aerosol spray of HDEF5 given through the nose and throat, once to several times a day, may be a very efficient approach to prevent infection with SARA-CoV-2 as well as influenza A.
Referências	NIV, Y. Defensin 5 for prevention of SARS-CoV-2 invasion and Covid-19 disease. **Medical Hypotheses**, [United Kingdom], v. 143, p. 110244, Oct. 2020. Disponível em: https://doi.org/10.1016/j.mehy.2020.110244
Fonte	https://www.sciencedirect.com/science/article/pii/S0306987720326761

Atualizado em: 4 de março de 2022

Título	Coronavirus disease 2019 (COVID-19): role of chest CT in diagnosis and management
Autor(es)	Yan Li, Liming Xia
Resumo	The objective of our study was to determine the misdiagnosis rate of radiologists for coronavirus disease 2019 (COVID-19) and evaluate the performance of chest CT in the diagnosis and management of COVID-19. The CT features of COVID-19 are reported and compared with the CT features of other viruses to familiarize radiologists with possible CT patterns.
Referências	LI, Y.; XIA, L. Coronavirus disease 2019 (COVID-19): Role of chest CT in diagnosis and management. **American Journal of Roentgenology**, [USA], v. 214, n. 6, p. 1280–1286, 2020. Disponível em: https://doi.org/10.2214/AJR.20.22954.
Fonte	https://www.ajronline.org/doi/pdf/10.2214/AJR.20.22954

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Título	Understanding of COVID-19 based on current evidence
Autor(es)	Pengfei Sun, Xiaosheng Lu , Chao Xu , Wenjuan Sun, , Bo Pan
Resumo	Since December 2019, a series of unexplained pneumonia cases have been reported in Wuhan, China. On 12 January 2020, the World Health Organization (WHO) temporarily named this new virus as the 2019 novel coronavirus (2019-nCoV). On 11 February 2020, the WHO officially named the disease caused by the 2019-nCoV as coronavirus disease (COVID-19). The COVID-19 epidemic is spreading all over the world, especially in China. Based on the published evidence, we systematically discuss the characteristics of COVID-19 in the hope of providing a reference for future studies and help for the prevention and control of the COVID-19 epidemic.
Referências	SUN, P. *et al.* Understanding of COVID-19 based on current evidence. **J Med Virol.**, [USA], v. 92, n. 6, p. 548–551, 2020. Disponível em: https://doi.org/10.1002/jmv.25722.
Fonte	https://onlinelibrary.wiley.com/doi/epdf/10.1002/jmv.25722

Título	Genomic evidence for reinfection with SARS-CoV-2: a case study
Autor(es)	Richard L Tillett, Joel R Sevinsky, Paul D Hartley, Heather Kerwin, Natalie Crawford, Andrew Gorzalski, Chris Laverdure, Subhash C Verma, Cyprian C Rossetto, David Jackson, Megan J Farrell, Stephanie Van Hooser, Mark Pandori
Resumo	The degree of protective immunity conferred by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is currently unknown. As such, the possibility of reinfection with SARS-CoV-2 is not well understood. We describe an investigation of two instances of SARS-CoV-2 infection in the same individual.
Referências	TILLETT, R. L. *et al.* Genomic evidence for reinfection with SARS-CoV-2: a case study. **Lancet Infect Dis.**, [United Kingdom], p. S1473309920307647, Oct. 12, 2020. Disponível em: https://doi.org/10.1016/S1473-3099(20)30764-7.
Fonte	https://www.thelancet.com/action/showPdf?pii=S1473-3099%2820%2930764-7

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Título	Are SARS-CoV-2 reinfection and Covid-19 recurrence possible? a case report from Brazil
Autor(es)	Lívia Pimenta Bonifácio, Ana Paula Sulino Pereira, Daniel Cardoso de Almeida e Araújo,, Viviane da Mata Pasti Balbão,, Benedito Antônio Lopes da Fonseca,, Afonso Dinis Costa Passos, Fernando Bellissimo-Rodrigues
Resumo	With the large number of individuals infected and recovered from Covid-19, there is intense discussion about the quality and duration of the immunity elicited by SARS-CoV-2 infection, including the possibility of disease recurrence. Here we report a case with strong clinical, epidemiological and laboratorial evidence of, not only reinfection by SARS-CoV-2, but also clinical recurrence of Covid-19.
Referências	BONIFÁCIO, L. P. *et al.* Are SARS-CoV-2 reinfection and Covid-19 recurrence possible? a case report from Brazil. **Rev. Soc. Bras. Med. Trop.**, Uberaba, v. 53, p. e20200619, Sept. 18, 2020. Disponível em: https://doi.org/10.1590/0037-8682-0619-2020.
Fonte	https://www.scielo.br/pdf/rsbmt/v53/1678-9849-rsbmt-53-e20200619.pdf

Título	Newcastle disease virus (NDV) expressing the spike protein of SARS-CoV-2 as a live virus vaccine candidate
Autor(ES)	Weina Suna , Sarah R. Leistg , Stephen McCroskerya , Yonghong Liua , Stefan Slamaniga , Justine Olivaa , Fatima Amanata,b , Alexandra Sch€ aferg , Kenneth H. Dinnon IIIg , Adolfo García-Sastrea,c,d,e , Florian Krammera , Ralph S. Baricf,g , Peter Palesea,c.
Resumo	Due to the lack of protective immunity of humans towards the newly emerged SARS-CoV-2, this virus has caused a massive pandemic across the world resulting in hundreds of thousands of deaths. Thus, a vaccine is urgently needed to contain the spread of the vírus.
Referências	SUN, W. *et al.* Newcastle disease virus (NDV) expressing the spike protein of SARS-CoV-2 as a live virus vaccine candidate. **EBioMedicine**, [Netherlands], v. 62, p. 103132, 2020. Disponível em: https://doi.org/10.1016/j.ebiom.2020.
Fonte	**https://www.thelancet.com/action/showPdf?pii=S2352-3964%2820%2930508-9**

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Título	Clinical recurrences of COVID-19 symptoms after recovery: viral relapse, reinfection or inflammatory rebound?
Autor(es)	Marie Gousseff , Pauline Penot , Laure Gallay , Dominique Batisse , Nicolas Benech , Kevin bouiller , Rocco Collarino , Anne Conrad , Dorsaf Slama , Cédric Joseph, Adrien Lemaignen , François-Xavier Lescure , Bruno Levy , Matthieu Mahevas, Bruno Pozzetto , Nicolas Vignier , Benjamin Wyplosz , Dominique Salmon , François Goehringer , Elisabeth Botelho-Nevers
Resumo	For the first 3 months of COVID-19 pandemic, COVID-19 was expected to be an immunizing non-relapsing disease. We report a national case series of 11 virologically-confirmed COVID-19 patients having experienced a second clinically- and virologically-confirmed acute COVID-19 episode. According to the clinical history, we discuss either re-infection or reactivation hypothesis. Larger studies including further virological, immunological and epidemiologic data are needed to understand the mechanisms of these recurrences.
Referências	GOUSSEFF, M. *et al.* Clinical recurrences of COVID-19 symptoms after recovery: Viral relapse, reinfection or inflammatory rebound? **The Journal of Infection**, Amsterdam, v. 81, n. 5, p. 816–846, 2020. Disponível em: https://doi.org/10.1016/j.jinf.2020.06.073.
Fonte	**https://pubmed.ncbi.nlm.nih.gov/32619697/**

Atualizado em: 4 de março de 2022

Título	On the potential role of exosomes in the COVID-19 reinfection/reactivation opportunity
Autor(es)	Fatma Elrashdy , Abdullah A Aljaddawi , Elrashdy M Redwan , Vladimir N Uversky
Resumo	We propose here that one of the potential mechanisms for the relapse of the COVID-19 infection could be a cellular transport pathway associated with the release of the SARS-CoV-2-loaded exosomes and other extracellular vesicles. It is possible that this "Trojan horse" strategy represents possible explanation for the re-appearance of the viral RNA in the recovered COVID-19 patients 7-14 day post discharge, suggesting that viral material was hidden within such exosomes or extracellular vesicles during this "silence" time period and then started to re-spread again.
Referências	ELRASHDY, F. *et al.* On the potential role of exosomes in the COVID-19 reinfection/reactivation opportunity. **Journal of Biomolecular Structure & Dynamics**, United Kingdom, p. 1–12, 2020. Disponível em: https://doi.org/10.1080/07391102.2020.1790426.
Fonte	https://doi.org/10.1080/07391102.2020.1790426

Título	COVID-19 Reinfection: myth or truth?
Autor(es)	Sayak Roy
Resumo	The novel coronavirus disease (COVID-19) has posed a large problem to this world and has exposed the skeleton of healthcare system all over. There have been reports of patients getting reinfected with COVID-19 as they tested positive for the virus again after discharge. We try to address the issue of this reinfection and want to clarify whether this entity actually exists or is it just a myth.
Referências	ROY, S. COVID-19 Reinfection: myth or truth? **SN Compr. Clin. Med**, Switzerland, n. 2, p. 710–713, 2020. Disponível em: https://doi.org/10.1007/s42399-020-00335-8.
Fonte	**https://pubmed.ncbi.nlm.nih.gov/32838134/**

Título	The SARS-CoV-2 outbreak: what we know
Autor(es)	Di Wu, Tiantian Wu, Qun Liu, Zhicong Yang
Resumo	There is a current worldwide outbreak of the novel coronavirus Covid-19 (coronavirus disease 2019; the pathogen called SARS-CoV-2; previously 2019-nCoV), which originated from Wuhan in China and has now spread to 6 continents including 66 countries, as of 24:00 on March 2, 2020. Governments are under increased pressure to stop the outbreak from spiraling into a global health emergency. At this stage, preparedness, transparency, and sharing of information are crucial to risk assessments and beginning outbreak control activities. This information should include reports from outbreak site and from laboratories supporting the investigation. This paper aggregates and consolidates the epidemiology, clinical manifestations, diagnosis, treatments and preventions of this new type of coronavirus.
Referências	WU, D. *et al.* The SARS-CoV-2 outbreak: what we know. **Int J Infect Dis.,** Netherlands, v. 94, p. 44–48, May 1, 2020. Disponível em: https://doi.org/10.1016/j.ijid.2020.03.004.
Fonte	**https://pubmed.ncbi.nlm.nih.gov/32171952/**

Título	Molecular basis of pathogenesis of coronaviruses: a comparative genomics approach to planetary health to prevent zoonotic outbreaks in the 21st century
Autor(es)	Purva Asrani, Gulam Mustafa Hasan, Sukhwinder Singh Sohal, Md. Imtaiyaz Hassan
Resumo	In the first quarter of the 21st century, we are already facing the third emergence of a coronavirus outbreak, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) responsible for the coronavirus disease 2019 (COVID-19) pandemic. Comparative genomics can inform a deeper understanding of the pathogenesis of COVID-19. Previous strains of coronavirus, SARS-CoV, and Middle-East respiratory syndrome-coronavirus (MERS-CoV), have been known to cause acute lung injuries in humans. SARS-CoV-2 shares genetic similarity with SARS-CoV with some modification in the S protein leading to their enhanced binding affinity toward the angiotensin-converting enzyme 2 (ACE2) receptors of human lung cells. This expert review examines the features of all three coronaviruses through a conceptual lens of comparative genomics. In particular, the life cycle of SARS-CoV-2 that enables its survival within the host is highlighted. Susceptibility of humans to coronavirus outbreaks in the 21st century calls for comparisons of the transmission history, hosts, reservoirs, and fatality rates of these viruses so that evidence-based and effective planetary health interventions can be devised to prevent future zoonotic outbreaks. Comparative genomics offers new insights on putative and novel viral targets with an eye to both therapeutic innovation and prevention. We conclude the expert review by (1) articulating the lessons learned so far, whereas the research is still being actively sought after in the field, and (2) the challenges and prospects in deciphering the linkages among multiomics biological variability and COVID-19 pathogenesis.
Referências	ASRANI, P. *et al.* Molecular Basis of Pathogenesis of Coronaviruses: A Comparative Genomics Approach to Planetary Health to Prevent Zoonotic Outbreaks in the 21st Century. **OMICS:** A Journal of Integrative Biology, India, v. 24, n. 11, p. 634–644, Nov. 4, 2020. Disponível em: https://doi.org/10.1089/omi.2020.0131.
Fonte	https://doi.org/10.1089/omi.2020.0131

Título	Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial
Autor(es)	Yanjun Zhang, Gang Zeng, Hongxing Pan, Changgui Li, Yaling Hu, Kai Chu, Weixiao Han, Zhen Chen, Rong Tang, Weidong Yin, Xin Chen, Yuansheng Hu, Xiaoyong Liu, Congbing Jiang, Jingxin Li, Minnan Yang, Yan Song, Xiangxi Wang, Qiang Gao†, Fengcai Zhu
Resumo	Background With the unprecedented morbidity and mortality associated with the COVID-19 pandemic, a vaccine against COVID-19 is urgently needed. We investigated CoronaVac (Sinovac Life Sciences, Beijing, China), an inactivated vaccine candidate against COVID-19, containing inactivated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), for its safety, tolerability and immunogenicity.
Referências	ZHANG, Y. *et al.* Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. **Lancet Infect Dis.**, [China?], p. S1473309920308434, Nov. 17 , 2020. Disponível em: https://doi.org/10.1016/S1473-3099(20)30843-4.
Fonte	**https://www.thelancet.com/action/showPdf?pii=S1473-3099%2820%2930843-4**

Título	SARS-CoV-2 seroprevalence and transmission risk factors among high-risk close contacts: a retrospective cohort study
Autor(es)	Oon Tek Ng, Kalisvar Marimuthu, Vanessa Koh, Junxiong Pang, Kyaw Zaw Linn, Jie Sun, Liang De Wang, Wan Ni Chia, Charles Tiu, Monica Chan, Li Min Ling, Shawn Vasoo, Mohammad Yazid Abdad, Po Ying Chia, Tau Hong Lee, Ray Junhao Lin, Sapna P Sadarangani, Mark I-Cheng Chen, Zubaidah Said, Lalitha Kurupatham, Rachael Pung, Lin-Fa Wang, Alex R Cook, Yee-Sin Leo, Vernon JM Lee.
Resumo	The proportion of asymptomatic carriers and transmission risk factors of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) among household and non-household contacts remains unclear. In Singapore, extensive contact tracing by the Ministry of Health for every diagnosed COVID-19 case, and legally enforced quarantine and intensive health surveillance of close contacts provided a rare opportunity to determine asymptomatic attack rates and SARS-CoV-2 transmission risk factors among community close contacts of patients with COVID-19.
Referências	NG, O. T. *et al*. SARS-CoV-2 seroprevalence and transmission risk factors among high-risk close contacts: a retrospective cohort study. **Lancet Infect Dis.**, Singapore , p. S1473309920308331, Nov. 2, 2020. Disponível em: https://doi.org/10.1016/S1473-3099(20)30833-1.
Fonte	https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30833-1/fulltext

Título	The correspondence between the structure of the terrestrial mobility network and the spreading of COVID-19 in Brazil
Autor(es)	Vander Luis de Souza Freitas, Thais Cláudia Roma de Oliveira Konstantyner,Jeferson Feitosa Mendes,Cátia Souza do Nascimento Sepetauskas, Leonardo Bacelar Lima Santos
Resumo	The inter-cities mobility network is of great importance in understanding outbreaks, especially in Brazil, a continental-dimension country. We adopt the data from the Brazilian Ministry of Health and the terrestrial flow of people between cities from the Brazilian Institute of Geography and Statistics database in two scales: cities from Brazil, without the North region, and from the São Paulo State. Grounded on the complex networks approach, and considering that the mobility network serves as a proxy for the SARS-CoV-2 spreading, the nodes and edges represent cities and flows, respectively. Network centrality measures such as strength and degree are ranked and compared to the list of cities, ordered according to the day that they confirmed the first case of COVID-19. The strength measure captures the cities with a higher vulnerability of receiving new cases. Besides, it follows the interiorization process of SARS-CoV-2 in the São Paulo State when the network flows are above specific thresholds. Some countryside cities such as Feira de Santana (Bahia State), Ribeirão Preto (São Paulo State), and Caruaru (Pernambuco State) have strength comparable to states' capitals. Our analysis offers additional tools for understanding and decision support to inter-cities mobility interventions regarding the SARS-CoV-2 and other epidemics.
Referências	FREITAS, V. L. de S. *et al.* The correspondence between the structure of the terrestrial mobility network and the spreading of COVID-19 in Brazil. **Cad. Saúde Pública**, Rio de Janeiro, v. 36, n. 9, p. e00184820, 2020. Disponível em: https://doi.org/10.1590/0102-311x00184820.
Fonte	https://scielosp.org/pdf/csp/2020.v36n9/e00184820/en

Título	Prospects for a safe COVID-19 vaccine
Autor(es)	Barton F. Haynes, Lawrence Corey, Prabhavathi Fernandes, Peter B. Gilbert, Peter J. Hotez, Srinivas Rao, Michael R. Santos, Hanneke Schuitemaker, Michael Watson, Ann Arvin.
Resumo	Rapid development of an efficacious vaccine against the viral pathogen severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the cause of the coronavirus disease 2019 (COVID-19) pandemic, is essential, but rigorous studies are required to determine the safety of candidate vaccines. Here, on behalf of the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Working Group, we evaluate research on the potential risk of immune enhancement of disease by vaccines and viral infections, including coronavirus infections, together with emerging data about COVID-19 disease. Vaccine-associated enhanced disease has been rarely encountered with existing vaccines or viral infections. Although animal models of SARS-CoV-2 infection may elucidate mechanisms of immune protection, we need observations of enhanced disease in people receiving candidate COVID-19 vaccines to understand the risk of immune enhancement of disease. Neither principles of immunity nor preclinical studies provide a basis for prioritizing among the COVID-19 vaccine candidates with respect to safety at this time. Rigorous clinical trial design and postlicensure surveillance should provide a reliable strategy to identify adverse events, including the potential for enhanced severity of COVID-19 disease, after vaccination.
Referências	HAYNES, B. F. *et al.* Prospects for a safe COVID-19 vaccine. ***Sci. Transl. Med***., Washington, DC, v. 12, n. 568, p. eabe0948, Nov. 4, 2020. Disponível em: https://doi.org/10.1126/scitranslmed.abe0948.
Fonte	**https://stm.sciencemag.org/content/12/568/eabe0948/tab-pdf**

Título	Prothrombotic autoantibodies in serum from patients hospitalized with COVID-19
Autor(es)	Yu Zuo , Shanea K. Estes , Ramadan A. Ali , Alex A. Gandhi, Srilakshmi Yalavarthi, Hui Shi, Gautam Sule , Kelsey Gockman , Jacqueline A. Madison , Melanie Zuo, Vinita Yadav, Jintao Wang , Wrenn Woodard , Sean P. Lezak, Njira L. Lugogo, Stephanie A. Smith , James H. Morrissey, Yogendra Kanthi, Jason S. Knight.
Resumo	Patients with COVID-19 are at high risk for thrombotic arterial and venous occlusions. Lung histopathology often reveals fibrin-based blockages in the small blood vessels of patients who succumb to the disease. Antiphospholipid syndrome is an acquired and potentially life-threatening thrombophilia in which patients develop pathogenic autoantibodies targeting phospholipids and phospholipid-binding proteins (aPL antibodies). Case series have recently detected aPL antibodies in patients with COVID-19. Here, we measured eight types of aPL antibodies in serum samples from 172 patients hospitalized with COVID-19. These aPL antibodies included anticardiolipin IgG, IgM, and IgA; anti–β2 glycoprotein I IgG, IgM, and IgA; and anti-phosphatidylserine/prothrombin (aPS/PT) IgG and IgM. We detected aPS/PT IgG in 24% of serum samples, anticardiolipin IgM in 23% of samples, and aPS/PT IgM in 18% of samples. Antiphospholipid autoantibodies were present in 52% of serum samples using the manufacturer's threshold and in 30% using a more stringent cutoff (≥40 ELISA-specific units). Higher titers of aPL antibodies were associated with neutrophil hyperactivity, including the release of neutrophil extracellular traps (NETs), higher platelet counts, more severe respiratory disease, and lower clinical estimated glomerular filtration rate. Similar to IgG from patients with antiphospholipid syndrome, IgG fractions isolated from patients with COVID-19 promoted NET release from neutrophils isolated from healthy individuals. Furthermore, injection of IgG purified from COVID-19 patient serum into mice accelerated venous thrombosis in two mouse models. These findings suggest that half of patients hospitalized with COVID-19 become at least transiently positive for aPL antibodies and that these autoantibodies are potentially pathogenic.
Referências	ZUO, Y. *et al.* Prothrombotic autoantibodies in serum from patients hospitalized with COVID-19. ***Sci. Transl. Med.***, Washington, DC, v. 12, n. 570, p. eabd3876, Nov. 18, 2020. Disponível em: https://doi.org/10.1126/scitranslmed.abd3876. Acesso em: nov. 26, 2020.
Fonte	**https://stm.sciencemag.org/content/12/570/eabd3876/tab-pdf**

Título	Transmission heterogeneities, kinetics, and controllability of SARS-CoV-2
Autor(es)	Kaiyuan Sun, Wei Wang, Lidong Gao, Yan Wang, Kaiwei Luo, Lingshuang Ren, Zhifei Zhan, Xinghui Chen, Shanlu Zhao, Yiwei Huang, Qianlai Sun, Ziyan Liu, Maria Litvinova, Alessandro Vespignani, Marco Ajelli, Cécile Viboud, Hongjie Yu
Resumo	A long-standing question in infectious disease dynamics concerns the role of transmission heterogeneities, driven by demography, behavior and interventions. Based on detailed patient and contact tracing data in Hunan, China we find 80% of secondary infections traced back to 15% of SARS-CoV-2 primary infections, indicating substantial transmission heterogeneities. Transmission risk scales positively with the duration of exposure and the closeness of social interactions and is modulated by demographic and clinical factors. The lockdown period increases transmission risk in the family and households, while isolation and quarantine reduce risks across all types of contacts. The reconstructed infectiousness profile of a typical SARS-CoV-2 patient peaks just before symptom presentation. Modeling indicates SARS-CoV-2 control requires the synergistic efforts of case isolation, contact quarantine, and population-level interventions, owing to the specific transmission kinetics of this virus.
Referências	SUN, K. *et al.* Transmission heterogeneities, kinetics, and controllability of SARS-CoV-2. ***Sciense***, Washington, DC, v. 370, n. 6520, p. eabe2424, Nov. 27, 2020. Disponível em: https://doi.org/10.1101/2020.08.09.20171132.
Fonte	https://science.sciencemag.org/content/early/2020/11/23/science.abe2424