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Main aspects and prophylactic measures of COVID-19 in Brazil

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ABSTRACT

From the first case of COVID-19 in Brazil, the country became the third in the world in the raking of cases and deaths. Despite the measures implemented by the government, the number of infected and killed by COVID-19 continues to increase and the country faces several other problems that include social and political aspects, making it difficult to contain the pandemic. The present study addressed the general characteristics of SARS-CoV-2, pointed out the main socio-epidemiological aspects in Brazil and the treatment of COVID 19. A literature review was carried out to search for articles in PubMed, Scielo and Google Scholar databases. Patients with COVID-19 may be asymptomatic, but among symptomatic patients, the severity of the disease is related to age and pre-existing medical conditions. The lungs are the organs most affected by the virus and, for this reason, respiratory manifestations such as cough, shortness of breath, sputum production, sore throat and nasal congestion are the symptoms most associated with COVID-19. The transmission of SARS-CoV-2 between humans occurs mainly through respiratory droplets, but they can also occur through contact with contaminated surfaces. Vaccine tests were carried out approved by the World Health Organization (WHO). Brazil stands out in second world position, with four approved vaccines: Pfizer-BioNTech, Oxford-AstraZeneca, CoronaVac (Sinovac), Janssen/Covishield.

Keywords: Coronavirus; pandemics; severe acute respiratory syndrome; epidemiology.

INTRODUCTION

The coronaviruses affect humans and animals worldwide, due to genetic variability and the high rate of recombination[1].

The coronavirus 2 disease (COVID-19) is caused by SARS-CoV-2. As of January 2021, this virus had infected more than eighty-seven million people worldwide and caused more than one million deaths. The pandemic reached Latin America in mid-2020. Brazil has stood out as the country with the highest number of cases and deaths in Latin America[2].

By January 10, 2021, more than 8 million cases had been registered in Brazil, with 62,290 new cases (incidence of 3843.0) and 202,631 accumulated deaths (2.5% lethality and mortality of 96.4). The city of São Paulo is the most populous in Brazil and has the highest number of cases and deaths[3]. Despite the measures implemented by the government, the number of people infected and killed by COVID-19 continues to increase and the country faces several other problems that include social and political aspects, making it difficult to contain the pandemic.

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Given this scenario, the current review study aimed to address the general characteristics of SARS-CoV-2 and to point out the main socio-epidemiological aspects of COVID-19 in Brazil.

METHODS

A literature review was carried out to search for articles in PubMed, SciELO, and Google Scholar databases until January 10, 2021. For the searches, the following keywords were used: ''COVID-19", ''SARS-CoV-2", ''Infection", "pathogenesis", "dissemination", "transmission", "clinical symptoms", "diagnosis", "treatment", and "Brazil", with interposition by the Boolean operator ''AND". We also retrieved the full text of the relevant cross-references from the search results. In addition, we accessed the scientific literature currently available in English and Portuguese and recommendations from the WHO Disease Centers, the Brazilian Ministry of Health, and the Brazilian Society of Infectious Diseases.

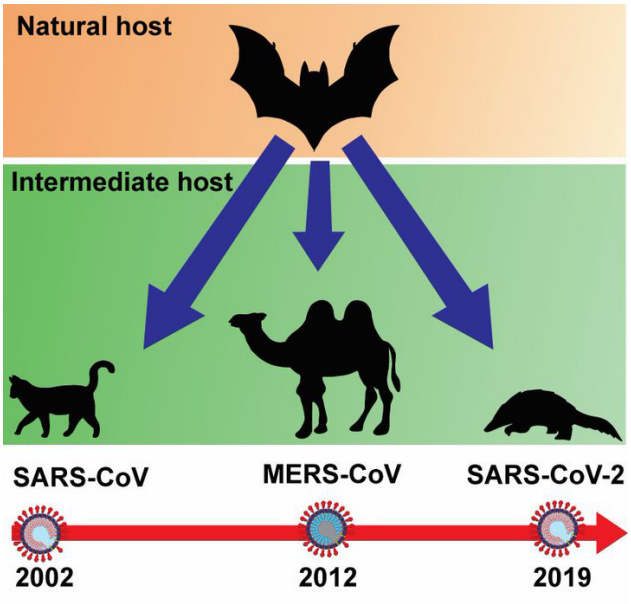

Figure 1: Hypotheses of natural hosts (bats) and pandemic intermediates caused by coronavirus in 2002 (SARS-COV: felines); 2012 (MERS-CoV: camels; 2019 (SARS-Cov-2: Mayan pangolin).

MAIN CHARACTERISTICS OF SARS-COV-2

The History of COVID-19

An outbreak of pneumonia was reported in Wuhan, Hubei Province, China in December 2019, and the World Health Organization (WHO) declared a Public Health Emergency of International Interest. The lower respiratory tract infection, COVID-19, has been linked to a new coronavirus, SARS-CoV-2[4].

Although it was suggested that the first cases of COVID-19 were linked to the Wuhan seafood market, studies found that 14 cases out of 41 patients were not related to these locations. In addition, none of these patients reported contact with bats, one of the SARS-CoV-2 hosts[5]. Later studies suggested the Malaysian pangolin (*Manis javanica*) as an intermediate host of the new coronavirus[6] (Figure 1). However, controversies exist and studies are needed to help understand the origin and intermediate transmission of SARS-CoV-2[5].

The first case of COVID-19 in Latin America occurred on February 25, 2020, in São Paulo, through the importation of the virus from northern Italy. Since then Brazil has presented the highest number of reported cases in Latin America[7].

Despite the confirmation of the first COVID-19 case in Brazil at the end of February 2020, the linear regression analysis made it possible to estimate the date of the beginning of the circulation and transmission of the virus. Studies show that probably the virus could already have been circulating among the population between late January and early February. This assumption is due to the 1% mortality rate and the number of deaths during the first two weeks after the Brazilian government implemented measures of social distance[8].

COVID-19

Clinical characteristics of COVID-19

The spectrum of clinical presentations of COVID-19 is broad, and some patients may be asymptomatic carriers and facilitate viral spread. Symptomatic cases are the most worrying, as the clinical presentations can range from mild symptoms, such as a common cold, to severe symptoms, with complications involving respiratory, neurological, and thrombotic manifestations, among others[9].

The lungs are the organs most affected by the virus and, for this reason, respiratory manifestations such as cough, shortness of breath, sputum production, sore throat, and nasal congestion are the symptoms most associated with COVID-19[10]. Autopsies performed on COVID-19 patients found multiple lesions in the epithelial cells that line the pulmonary alveoli, leading to a reduction in oxygenation and consequent respiratory insufficiency. When infected, lysed epithelial cells leave the basement membrane exposed, initiating the coagulation cascade, leading to thrombus formation that obstructs pulmonary vessels, preventing the passage of oxygen to small arteries[11].

Studies have demonstrated the relationship between the presence of the virus and the high mortality caused by coagulation complications in patients. In the results, patients presented abnormal intravascular coagulation, where those who died presented greater complications. Tang et al.[12] reported that 71.40% of non-survivors presented abnormal intravascular coagulation.

There are indications that even without presenting the characteristic symptoms of respiratory manifestations or the other

complications mentioned, patients may experience a sudden loss of taste and smell, these being considered early markers of infection[13]. It is believed that there may be direct damage to olfactory receptor neurons located in the olfactory epithelium, as these cells express the protein receptors used in the SARS-CoV-2 invasion mechanism. If these receptors show neural expression, the virus can access the nervous system through the nasal mucosa and, once in the central nervous system, could reach the brain stem and be responsible for pulmonary complications[14].

A study that documented the comorbidities associated with the severity of COVID-19 in the 26 Brazilian states and the Federal District pointed out chronic heart diseases, diabetes, and chronic lung diseases (including chronic obstructive pulmonary disease and asthma) as the main comorbidities associated with death, followed by chronic kidney disease, stroke, hypertension, obesity, and immunosuppressive diseases as the most prevalent. This study pointed out that male individuals and those over 60 years old were most affected, data that are in agreement with reports from other countries[15].

Thus, infection by SARS-CoV-2 involves multiple tissues, and its symptoms may vary according to the tissue's sensitivity to infection. In addition to common symptoms such as fever and respiratory symptoms, COVID-19 infection can produce several extra-respiratory manifestations that lead to aggravation of the clinical condition of these patients. Further studies are needed to understand tissue damage in asymptomatic patients.

Methods for detecting COVID-19

The rapid spread of COVID-19 is one of the biggest problems, contributing to its proliferation in only a few days. For this problem to be controlled, a fast and accurate diagnosis is crucial. Currently, the diagnosis is made from the patient's history, clinical manifestations, serology, molecular diagnosis, and computed tomography[16].

Depending on the severity of the disease, laboratory tests undergo changes that may include: lymphopenia, thrombocytopenia and leukopenia, as well as changes in C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum ferritin, interleukin-6 (IL6), lactate dehydrogenase (LDH), creatine kinase (CK), alanine aminotransferase (ALT) and aspartate aminotransferase (AST)[16]. In addition, changes in coagulation factors are observed: prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen and D-dimer, which is responsible for the activity of the fibrinolytic system, and when elevated it becomes an independent risk factor for the respiratory syndrome. In critically ill patients, the D-dimer is elevated and the prothrombin and thromboplastin time is reduced. Platelet count can also be reduced[17].

Computed tomography (CT) is another parameter used in the diagnosis of COVID-19, however, it cannot confirm or exclude it in isolation[17]. It can usually present multifocal ground-glass opacities, close to the peripheral sections of the lungs. As the disease progresses, it is noted that they manifest by extension and increase in the density of opacities, which may be associated with fine crosslinking, vascular thickening and reverse halo sign. Asymptomatic individuals may present pulmonary findings less frequently than symptomatic patients and, in general, with less extensive involvement and predominant ground-glass opacities. On the other hand, symptomatic patients usually present pulmonary findings, with predominant consolidations and more extensive parenchymal involvement[17].

Serological tests measure the host's immune system response to infection. Blood IgG and IgM antibody tests become detectable after 4-5 days of infection. The method used is the conventional ELISA which produces the result in a short time. However, this method may present low specificity, and the molecular biology test is more recommended to confirm the diagnosis in this period, in order to detect the circulating viral load[18].

Currently the cell biology test is the most highly recommended for the diagnosis of COVID-19. RT-PCR can be used to confirm suspected cases, release patients from quarantine, and screen for asymptomatic patients who have had close contact with people who tested positive for COVID-19[19]. Several RT-PCR protocols have been proposed following the guidelines of the WHO (World Health Organization) and KCDC (Korea Centers for Disease Control and Prevention), which recommend amplification of the E, N and RdRp genes. When the protocols do not use these genes, the recommendation is that all the researched genes be detected to confirm the result[20].

Sample collections of patients with severe symptoms are via nasopharyngeal swab, oropharyngeal swab, nasopharyngeal, sputum, bronchial lavage, tracheal aspirates, bronchoalveolar lavage, and transbronchial lung biopsy. The collection of samples from patients with mild symptoms or asymptomatic patients is performed through nasopharyngeal and oropharyngeal swabs, which must be placed together in the same viral transport medium (VTM) to increase sensitivity[21]. If the RT-PCR test is negative and clinical suspicion persists, the test should be repeated, obtaining swab samples from other sites in the respiratory tract[17].

Dissemination

The main form of transmission is through the aerosol route, particles small enough to be airborne, such as drops of saliva projected by sneezing[22].

Studies point to the permanence of the virion on various surfaces, such as plastics, steel, and cardboard, among others, and the viability of the viral particle on these surfaces is, respectively, 72, 48, and 24 hours. This characteristic increases indirect contamination rates, where there is no direct contact with the infected patient[23].

Due to the possibility of excretion of SARS-CoV-2 in feces, a study group has been attempting to detect this virus in sewage samples, aiming to check the viral load in different regions[24]. Another concern is related to the interconnectivity of the wastewater pipeline network inside buildings or between buildings, as defects in the pipeline can contribute to the transport through aerosols. In 2003, plumbing defects together with bathroom ventilation were responsible for the spread of SARS-CoV in a 50-story building, with 342 cases and 42 deaths from acute respiratory syndrome. Currently, this event is worrying, especially in environments with a high risk of transmission of SARS-CoV-2, such as hospitals and health buildings[25].

It is noted that environmental factors can affect viral spread. Although it has been suggested that a higher temperature was detrimental to the viability of the viral particle, a Brazilian study verified the temperature in all regions of the country with cases of COVID-19 and failed to demonstrate a negative effect in the detection by SARS-Cov-2 at temperatures[26] above 25°C. Further studies are needed to evaluate the infectivity of SARS-Cov-2 against environmental factors, such as temperature range, air pollution, and relative humidity, especially in tropical countries.

Social distancing was a measure used worldwide to decrease viral spread. The Ministry of Health[3] in Brazil recommended maintaining a minimum distance of 1 meter between people in public and social places and avoiding unnecessary physical contact. In addition, hygiene measures and the use of masks as physical barriers were recommended, as well as quarantine, which was managed according to each Brazilian State, aiming to reduce viral circulation and the future resumption of activities and economic aspects.

Epidemiology in Brazil

In Brazil, the Ministry of Health website has created an internet web COVID-19 portal, where data in reported is the number of infections and deaths per 100 thousand inhabitants are disseminated daily[3]. Since the confirmation of the first case in Brazil, the COVID-19 Portal has been counting more and more notifications, and by January 2021, Brazil was ranked as the country with the third-highest number of cases and deaths in the world (8,075,998 cases and 202.631 deaths on January 10, 2021), behind only the United States and India, which account for more than 10 million cases[2,3].

São Paulo is the most populous city in South America and had recorded more than one million cases and more than 48 thousand deaths by January 2021. In second place is Bahia, followed by the State of Minas Gerais[3] (Figure 2).

It is worth mentioning that throughout the country the molecular diagnosis was performed only in severe cases of COVID-19, and the data presented on the COVID-19 Portal may be underestimated. The high rate of undiagnosed patients can negatively affect disease control and the country's economy due to the increase in the period of social isolation[27].

Brazil has many risk groups, such as the elderly, patients with comorbidities and a mixed population that includes African, Caucasian and indigenous characteristics. Due to genetic diversity, the response to COVID-19 differs in each region of Brazil. The immunological response of indigenous citizens to SARS-CoV-2 is not known and medical care should be prioritized in this population[27].

Linked to genetic characteristics, there are background economic factors that contribute to a need for different medical and social care in each area. Indigenous people live in regions with greater restrictions for access to health and the diagnosis of COVID-19. Low-income urban conglomerates, known as "favelas", contain many people living in precarious health conditions, which contributes to viral transmission due to the low availability of diagnostic tests, number of ICUs, and adequate management of infected patients.

WHO recommends 1 to 3 ICU beds for every 10,000 inhabitants, but Brazil provides approximately 1 bed for every 10,000 inhabitants, distributed unevenly between Brazilian regions and between the public and private health systems[28]. In addition, since the beginning of the pandemic in Brazil, there have been three ministers of health, which has generated political conflicts and made it difficult to target effective measures in the area of health, increasing inequality between Brazilian states in combating COVID-19.

Treatments for COVID-19

As COVID-19 is an emerging acute respiratory infectious disease, in a short time researchers around the world began to present possible therapies for the disease, and doctors began to suggest many treatments empirically, together (or not) with research, in the hope that something would soon be effective[29].

For 20 years, chloroquine, a drug which includes phagolysosomal alkalinization among its activities - which hinders the steps of viral replication dependent on low pH, fusion, and coating - was tested in viral infections because it has been demonstrated, *in vitro*, to be effective against a variety of viruses[30]. As it is used to treat diseases such as lupus for example, and is consequently easy to access, in addition to low cost, chloroquine has gained great space as a strong fighter against the epidemic of the new coronavirus. Some authors[30] faithfully defend the established safety of chloroquine as well as hydroxychloroquine.

On April 1, 2020, the Ministry of Health released an information note, based on Law No. 13.979, making chloroquine available nationwide as adjuvant therapy in the treatment of confirmed cases of the new coronavirus. This measure could be modified at any time, but the decision was initially made based on publications

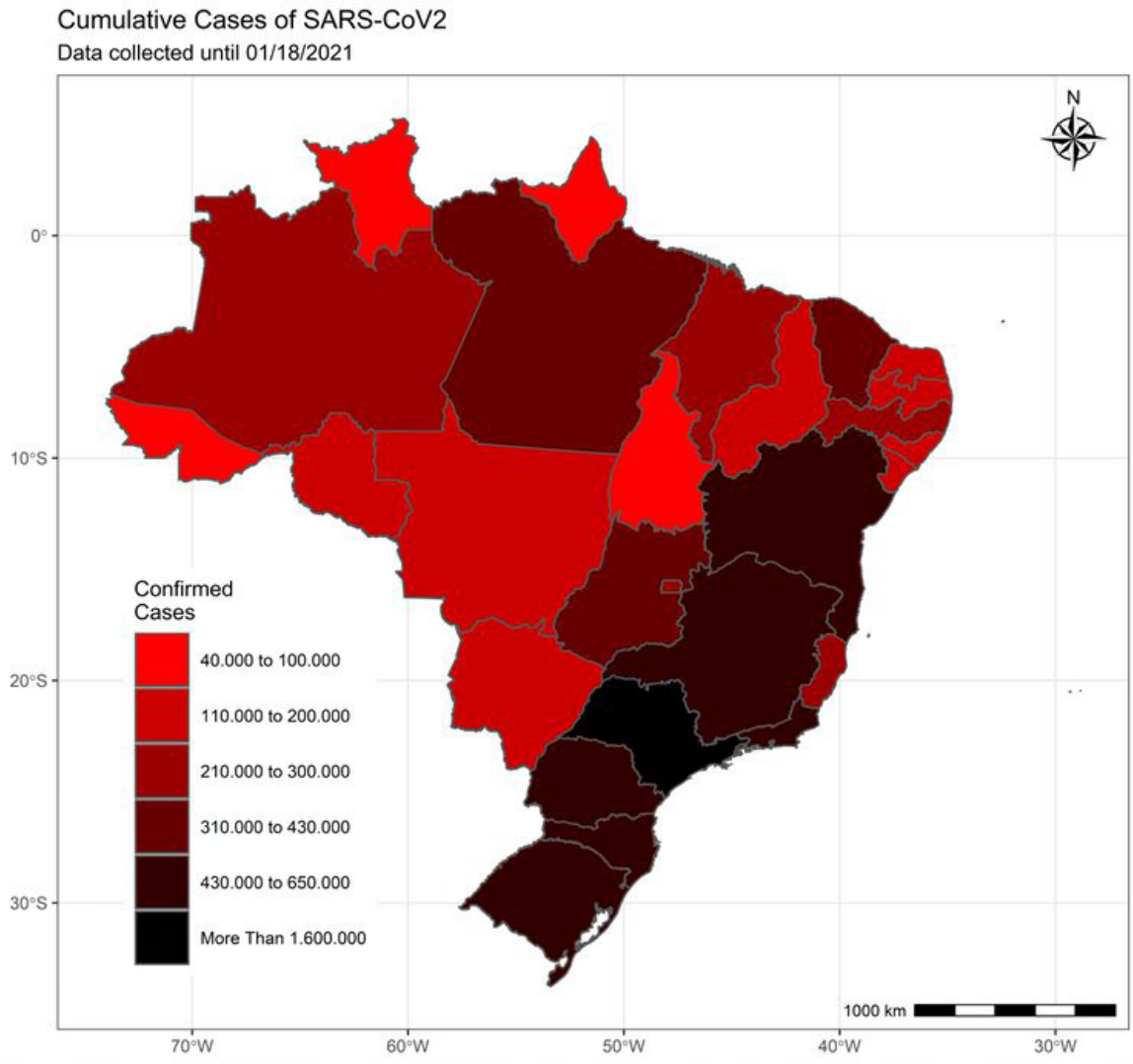

Figure 2: Cumulative cases of SARS-CoV2 in Brazil (data collected until 01/18/2021).

that present experimentation and systematization of tests that resulted in the inhibition of the virus six days after its confirmation in the patient. However, the measure is still at the discretion of the medical team[31].

Although the WHO declared that the entire country is sovereign to decide on clinical protocols for the use of medicines, it emphasized that there is no evidence that chloroquine and hydroxychloroquine are effective and safe in the treatment of COVID-19. In addition, in June 2020 clinical trials involving these drugs were stopped due to lack of proof of efficacy in the treatment of viral disease and the following month the Brazilian Society of Infectology warned that these drugs should be withdrawn immediately from all phases of COVID-19 treatment[32].

Although chloroquine and hydroxychloroquine did not show satisfactory results in a multicenter study conducted in Brazilian hospitals[33], medical prescription continues in the country, along with other drugs, such as ivermectin and azithromycin.

Ivermectin is an antiparasitic that has demonstrated antiviral action against SARS-CoV-2 *in vitro*. The study proved the inhibition of viral replication with a single dose in the period of 24 to 48 hours and, according to the authors, the drug may have inhibited importin-α/β mediated nuclear import, but no *in vivo* studies have been carried out. Authors emphasize that well-conducted clinical trials are needed to validate the impact before implementing the use of ivermectin in the treatment of COVID-19[34].

It is important to be very cautious in relation to the disclosure of data on the possible action of ivermectin against SARS-CoV-2, to avoid the increase in demand and self-medication. In Brazil, the disclosure of preliminary findings of a potential effect of hydroxychloroquine combined with azithromycin against the new

coronavirus resulted in a lack of stock of the drug for other clinical conditions, such as malaria, rheumatoid arthritis, and systemic lupus erythematosus[34].

There is still controversy in the performance of antivirals against the coronavirus because of the response to SARS-CoV-2, therefore, some, already tested, seem to be more efficient while others remain under investigation. In this case, the following have been approved: Lopinavir/Ritonavir which act as protease inhibitors used to treat human immunodeficiency virus (HIV) infection and have shown a decrease in viral β-coronavirus loads[22]. Combination of Ribavirin with Lopinavir/Ritonavir[35], used mainly for the treatment of Hepatitis C, has demonstrated interference in the synthesis of viral mRNA of the new coronavirus[2]; and some drugs like Oseltamivir, Ganciclovir, and Penciclovir/Aciclovir that have been approved but are not yet considered fully valid for COVID-19[2].

The antiviral Remdesivir, used to treat Ebola, has attracted attention, because it has broad activity against various RNA viruses. Even though it has been successful in intravenous treatment in the first case of COVID-19 in the USA, its effectiveness is still being tested, since the decision to use Remdesivir in the case cited was based on the worsening of the patient's clinical status[36]. In other studies, there is already a notable interference in the nsp12 polymerase of SARS-CoV-2, which is an important target for inhibiting the virus.

In Brazil, the Ministry of Health website makes available access to manuals, guides, and guidelines for the Diagnosis and Treatment of the new coronavirus. The Ministry also makes available an image bank to support the care of cases, which enables sharing among health professionals with access to the platform, which can be entered through a register that keeps the service available every hour and day of the week, aiming to contribute to and help the frontline community[37].

In the state of São Paulo, the Butantã Institute, in partnership with the pharmaceutical company Sinovac Life Science, Life Science carried out the final tests of the Coronavac vaccine. The partnership was signed on June 11 and provides for testing on 9 thousand Brazilian volunteers by June 2021, aiming at production on an industrial scale to be provided free of charge to the population by the Brazilian Health System (SUS). Phase 1 of the test started with 144 Chinese individuals to gather evidence on safety. Phase 2 was carried out on 600 Chinese volunteers to verify the immune response of the volunteers, and phase 3 is being completed on 9 thousand Brazilian volunteers in which the safety and efficacy of the vaccine against COVID-19 are being verified[38].

The World Health Organization (WHO) has authorized the emergency use of the Janssen COVID19 vaccine (Ad26. COV2-S, recombinant), developed by Janssen, (pharmaceutical division from Johnson & Johnson) in all countries: February 27, 2021 in United States; March 5, 2021 in Canada and March 11, 2021 in Europe[39].

In Brazil, the request made by the company occurred on March 24, 2021. With this approval, Brazil stands out in second world position, with four approved vaccines: Pfizer-BioNTech, Oxford-AstraZeneca, CoronaVac (Sinovac), Janssen/Covishield[39].

After experiments, Anvisa concludes that the Janssen vaccine protects against the severe form of the disease and is effective in preventing Covid-19 in adult patients, however, it does not authorize the importation of 20 million doses of the Covaxin vaccine, manufactured in India, through the evaluation of technical information related to the inspection of Good Manufacturing Practices (GMP) at the manufacturer Bharat Biotech International Limited, at the manufacturer Bharat and for not presenting a technical report on the evaluation of the vaccine issued by the health authority of India, in disagreement with § 3 of art. 16 of Brazilian Law 14.124/2021[39].

Conclusion

The COVID-19 pandemic affected countries worldwide, but Brazil, due to social, ecological and political aspects, was one of the most affected, being the second country with the highest number of cases and deaths in the world.

It is necessary to raise awareness of the importance of vaccination, stressing that companies that manufacture the drug or vaccine against Covid-19, must present results to Anvisa and request health registration in Brazil, in accordance with current health legislation.

Reinforce protective measures, such as social distance, hygiene and the use of masks for individual protection and special attention to others, paying attention to the viral spread among family members, neighbors and other close people.

Although there are contradictions between measures taken by politicians and measures advocated by science against coronaviruses, it should be noted that virologists and scientists from around the world are working to develop therapies against SARS-CoV-2. Meanwhile, hygienic precautionary measures and social distancing must be followed.

The conflicts between politics and science have generated a health crisis throughout Brazil. Although research incentives and funding in Brazil have been cut in recent years, the country is forced to invest in science to seek treatment alternatives and effective vaccines to contain COVID-19. Despite the conflict between the government, specialists, and health organizations, investment in research is necessary and urgent so that Brazil can control viral transmission and resume the economy consciously and safely.

REFERENCES

1. Hussain A, Bhowmik B, Moreira NCV. COVID-19 and diabetes: Knowledge in progress. Diabetes Res Clin Pract. 2020;162:108142. https://doi.org/10.1016/j.diabres.2020.108142

2. World Health Organization (WHO). WHO Coronavirus Disease (COVID-19) Dashboard. Available from: https://covid19.who.int/

3. 'Brasil. Ministério da Saúde. Coronavírus Brasil. Covid-19: Painel coronavirus. Available from: https://covid.saude.gov.br/

4. Ye ZW, Yuan S, Yuen KS, Fung SY, Chan CP, Jin DY. Zoonotic origins of human coronaviruses. Int J Biol Sci. 2020;16(10):1686-97. https://doi.org/10.7150/ijbs.45472

5. Malaiyan J, Arumugam S, Mohan K, Radhakrishnan GG. An update on the origin of SARS-CoV-2: Despite closest identity, bat (RaTG13) and pangolin derived coronaviruses varied in the critical binding site and O-linked glycan residues. J Med Virol. 2021;93(1):499-505. https://doi.org/10.1002/jmv.26261

6. Liu P, Jiang JZ, Wan XF, Hua Y, Li L, Zhou J, et al. Are pangolins the intermediate host of the 2019 novel coronavirus (SARS-CoV-2)? PLoS Pathog. 2020;16(5):e1008421. https://doi.org/10.1371/journal.ppat.1008421

7. Amaku M, Covas DT, Coutinho FAB, Azevedo Neto RS, Struchiner C, Wilder-Smith A, et al. Modelling the test, trace and quarantine strategy to control the COVID-19 epidemic in the state of São Paulo, Brazil. Infect Dis Model. 2021;6:46-55. https://doi.org/10.1016/j.idm.2020.11.004

8. Delatorre E, Mir D, Graf T, Bello G. Tracking the onset date of the community spread of SARS-CoV-2 in Western Countries. Mem Inst Oswaldo Cruz. 2020;115:e200183. https://doi.org/10.1590/0074-02760200183

9. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-13. https://doi.org/10.1016/S0140-6736(20)30211-7

10. Lai CC, Liu YH, Wang CY, Wang YH, Hsueh SC, Yen MY, et al. Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): Facts and myths. J Microbiol Immunol Infect. 2020;53(3):404-12. https://doi.org/10.1016/j.jmii.2020.02.012

11. Dolhnikoff M, Duarte-Neto AN, Monteiro RAA, Silva LFF, Oliveira EP, Saldiva PHN, et al. Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19. J Thromb Haemost. 2020;18(6):1517-9. https://doi.org/10.1111/jth.14844

12. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844-7. https://doi.org/10.1111/jth.14768

13. Lechien JR, Chiesa-Estomba CM, Siati DR, Horoi M, Le Bon SD, Rodriguez A, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol. 2020;277(8):2251-61. https://doi.org/10.1007/s00405-020-05965-1

14. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host-Virus Interaction, and Proposed Neurotropic Mechanisms. ACS Chem Neurosci. 2020;11(7):995-8. https://doi.org/10.1021/acschemneuro.0c00122

15. Pachiega J, Afonso AJDS, Sinhorin GT, Alencar BT, Araújo MDSM, Longhi FG, et al. Chronic heart diseases as the most prevalent comorbidities among deaths by COVID-19 in Brazil. Rev Inst Med Trop Sao Paulo. 2020;62:e45. https://doi.org/10.1590/S1678-9946202062045

16. Ge H, Wang X, Yuan X, Xiao G, Wang C, Deng T, et al. The epidemiology and clinical information about COVID-19. Eur J Clin Microbiol Infect Dis. 2020;39(6):1011-19. https://doi.org/10.1007/s10096-020-03874-z

17. Chate RC, Kaiser E, Nunes U, Bastos R, Passos D, Borges G, et al. Presentation of pulmonary infection on CT in COVID-19: initial experience in Brazil. J Bras Pneumol. 2020;46(2):e20200121. https://doi.org/10.36416/1806-3756/e20200121

18. Beeching NJ, Fletcher TE, Beadsworth MBJ. Covid-19: testing times. BMJ. 2020;369:m1403. https://doi.org/10.1136/bmj.m1403

19. Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DK, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill. 2020;25(3):2000045. http://dx.doi.org/10.2807/1560-7917.ES.2020.25.3.2000045

20. Martino F, Amici G, Grandesso S, Mortellaro RF, Lo Cicero A, Novara G. Analysis of the Clinical and Epidemiological Meaning of Screening Test for SARS-CoV-2: Considerations in the Chronic Kidney Disease Patients during the COVID-19 Pandemic. Int J Clin Med. 2021;10(5):1139. https://doi.org/10.3390/jcm10051139

21. Hong KH, Lee SW, Kim TS, Huh HJ, Lee J, Kim SY, et al. Guidelines for Laboratory Diagnosis of Coronavirus Disease 2019 (COVID-19) in Korea. Ann Lab Med. 2020;40(5):351-60. https://doi.org/ 10.3343/alm.2020.40.5.351

22. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Mil Med Res. 2020;7(1):11. https://doi.org/10.1186/s40779-020-00240-0

23. Fiorillo L, Cervino G, Matarese M, D'Amico C, Surace G, Paduano V, et al. COVID-19 Surface Persistence: A Recent Data Summary and Its Importance for Medical and Dental Settings. Int J Environ Res Public Health. 2020;17(9):3132. https://doi.org/10.3390/ijerph17093132

24. Bivins A, North D, Ahmad A, Ahmed W, Alm E, Been F et al. Wastewater-Based Epidemiology: Global Collaborative to Maximize Contributions in the Fight Against COVID-19. Environ Sci Technol. 2020;54(13):7754-7. https://doi.org/10.1021/acs.est.0c02388

25. Gormley M, Aspray TJ, Kelly DA. COVID-19: mitigating transmission via wastewater plumbing systems. Lancet Glob Health. 2020;8(5):e643. https://doi.org/ 10.1016/S2214-109X(20)30112-1

26. Prata DN, Rodrigues W, Bermejo PH. Temperature significantly changes COVID-19 transmission in (sub)tropical cities of Brazil. Sci Total Environ. 2020;729:138862. https://doi.org/10.1016/j.scitotenv.2020.138862

27. Marson FAL, Ortega MM. COVID-19 in Brazil. Pulmonology. 2020;26(4):241-4. https://doi.org/10.1016/j.pulmoe.2020.04.008

28. Palamim CVC, Marson FAL. COVID-19 - The Availability of ICU Beds in Brazil during the Onset of Pandemic. Ann Glob Health. 2020;86(1):100. https://doi.org/10.5334/aogh.3025

29. Palmeira VA, Costa LB, Perez LG, Ribeiro VT, Lanza K, Silva ACSE. Do we have enough evidence to use chloroquine/hydroxychloroquine as a public health panacea for COVID-19? Clinics. 2020;75:e1928. https://doi.org/10.6061/clinics/2020/e1928

30. Rodríguez-Morales AJ. Deep impact of COVID-19 in the healthcare of Latin America: the case of Brazil. Braz J Infect Dis. 2020;24(2):93-5. https://doi.org/10.1016/j.bjid.2020.04.005

31. Brasil. Ministério da Saúde. Secretaria de Ciência, Tecnologia e Insumos Estratégicos. Departamento de Assistência Farmacêutica e Insumos Estratégicos. Nota Informativa nº6/2020-DAF/SCTIE/MS. Brasília: Ministério da Saúde, 2020.

32. Sociedade Brasileira de Infectologia (SBI). Informe n° 16 da Sociedade Brasileira de Infectologia sobre: atualização sobre a Hidroxicloroquina no tratamento precoce da COVID-19. Available from: https://infectologia.org.br/wp-content/uploads/2020/07/atualizacao-sobre-a-hidroxicloroquina-no-tratamento-precoce-da-covid-19.pdf

33. Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Avezum A, et al. Coalition Covid-19 Brazil I Investigators. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. N Engl J Med. 2020;383:2041-52. https://doi.org/10.1056/NEJMoa2019014

34. Chaccour C, Hammann F, Ramón-García S, Rabinovich NR. Ivermectin and COVID-19: Keeping Rigor in Times of Urgency. Am J Trop Med Hyg. 2020;102(6):1156-7. https://doi.org/10.4269/ajtmh.20-0271

35. Zumla A, Chan JF, Azhar EI, Hui DS, Yuen KY. Coronaviruses - drug discovery and therapeutic options. Nat Rev Drug Discov. 2016;15(5):327-47. https://doi.org/10.1038/nrd.2015.37

36. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. Washington State 2019-nCoV Case Investigation Team. First Case of 2019 Novel Coronavirus in the United States. N Engl J Med. 2020;382(10):929-36. https://doi.org/10.1056/NEJMoa2001191

37. Brasil. Ministério da Saúde. Coronavírus. O que você precisa saber: como se proteger. Available from: https://coronavirus.saude.gov.br/

38. Governo do Estado de São Paulo. SP contra o novo coronavírus. Saiba como se proteger: vacina. Available from: https://www.saopaulo.sp.gov.br/coronavirus/

39. Brasil. Ministério da Saúde. Agência Nacional de Vigilância Sanitária (ANVISA). COVID 19, Coronavírus. Available from: http:www.gov.br/anvisa/pt-br/assuntos/paf/coronavirus