



HEALTH SCIENCES

COVID-19 pandemic outbreak: the Brazilian reality from the first case to the collapse of health services

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Abstract: Coronavirus is associated with several infectious diseases that cause outbreaks in humans, such as SARS in 2002-2003 and MERS in 2012. In December 2019, COVID-19, promoted by the SARS-CoV-2 virus, was first reported in Wuhan (China) as a new coronavirus disease. This outbreak quickly reached a pandemic status, affecting at least 185 countries and territories to date on all continents. The first case of COVID-19 reported in São Paulo city (Brazil) occurred in February 26th. Days later, 182 suspected cases in 16 states were being monitored. In May 30th, 514,849 cases and 29,314 deaths were confirmed in Brazil comprising all 26 states and Federal District. The primary measure in order to contain the spread of SARS-CoV-2 involved social isolation. At that time there were not enough diagnostic tests to identify infected individuals and data were strongly associated with sub notifications. Nevertheless, the effectiveness of this measure largely depends on the individual's social responsibility. This measure has a severe economic and social impact, as in other countries. In this review, we present an overview and scientific perspectives of the evolution of COVID-19 from Brazilian databases in which climate and economic situations differ from China, European countries, and the USA.

Key words: COVID-19, SARS-CoV-2, Pandemic, Brazil.

INTRODUCTION

Coronaviridae is a family of enveloped positive-stranded RNA viruses of vertebrates, introduced into humans from a zoonotic reservoir and which can promote a respiratory syndrome. In the past, the Severe Acute Respiratory Syndrome (SARS), with a fatality rate of around 10% (8,098 cases and 774 deaths), and the Middle East Respiratory Syndrome (MERS), around 34% (2,494 cases and 858 deaths) are the major representants of this virus family (Gorbalenya 2020, Mahase 2020). Currently, a new virus representative of this family, named SARS-CoV-2, has been promoted a worldwide pandemic outbreak, the 2019-nCoV (disused term) or COVID-19 disease. The human first cases were detected in Wuhan, China, in

November 2019, probably from a horseshoe bat contagion in Yunnan Province (Wang & Hu 2013, Murdoch & French 2020, Huang et al. 2020).

The COVID-19 growth curve in China was built through daily infographics (Figure 1), with an initial plateau in February 29th and new increase of confirmed cases and deaths in April 30th. The evidence of the pandemic could be observed in Figure 2, and 188 countries presented confirmed cases and elevated the number to more than six million people.

VIRUS CHARACTERIZATION AND CELL INTERACTION

SARS-CoV-2 is a positive single-stranded RNA virus ($(+)$ ssRNA) of approximately 29802 nucleotides

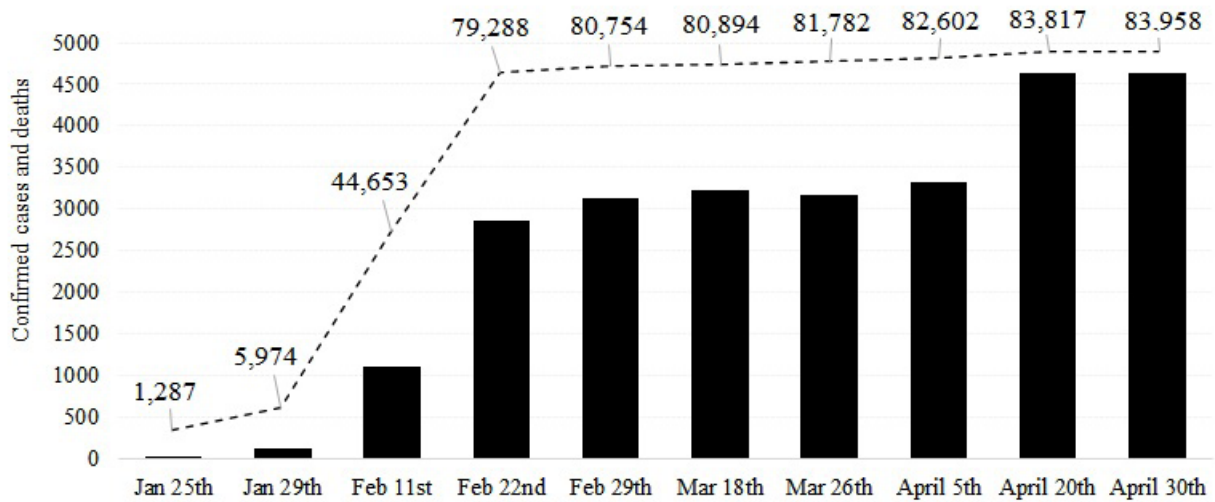


Figure 1. Briefing of daily infographics disclosed by China in the National Health Commission of the people's Republic of China, the last date available was in April 30th (<http://en.nhc.gov.cn/index.html>). Black vertical bars represent the total deaths by date, and the dotted line represents the number of cases by time.



Figure 2. Total worldwide confirmed cases and the most 10 countries affected by COVID-19 (The map was captured from the CDC website and while the data are contained on the National Center for Immunization and Respiratory Diseases (NCIRD) and Johns Hopkins University websites). Data recovered in June 6th, 7 p.m. Brasilia time).

(Wu et al. 2020). The virus genome consists of fourteen functional ORFs encoding three classes of proteins. Two large polyproteins (pp), pp1a and pp1ab, which are divided into sixteen non-structural proteins (nsps) necessary for viral RNA synthesis and blocking the innate immune response (nsp1; nsp18-2'-O-metil Transferase; nsp3-deubiquitinase). Four structural proteins

(S, E, M, and N), are essential for viral assembly and eight accessory proteins, which provide a selective advantage in the infected host (Decroly et al. 2011, Sevajol et al. 2014, Lehmann et al. 2015). For the synthesis of viral RNA within host cells, it is necessary to translate and assemble viral replicase complexes (Ziebuhr 2005, Ahn et al. 2012), producing genomic and

sub-genomic RNAs. Subgenomic RNAs serve as mRNAs of structural protein genes and the non-structural ones, which reside downstream of the polyproteins of the replicase (Jaimes et al. 2020). All positive sense subgenomic RNAs are 3' co-terminals with complete viral genome. Genomic and subgenomic RNAs are produced through negative chain intermediates (Kirchdoerfer & Ward 2019).

After successful replication and subgenomic RNA synthesis, structural proteins S, E, and M are translated and joined into the endoplasmic reticulum (Hu et al. 2017, 2018, Shi et al. 2018). Then, these proteins enter along the secretory pathway into the intermediate compartments of the endoplasmic-Golgi reticulum (Kim et al. 2020), they find viral genomes encapsulated by protein N and bind to form a complete virus. After assembly, viruses are transported to the cell surface in vesicles and released by exocytosis (Tang et al. 2020).

Some data have shown that COVID-19 has killed more people than SARS and MERS combined (Mahase 2020). Clinical signs and symptoms are clear now, after the experience of Chinese colleagues during the outbreak in China. Many studies are still correlating mechanisms of action used by the virus to understand aspects of SARS and MERS. Studies show that the mechanism of interacting of the virus with human cells is associated with the angiotensin-converting enzyme 2 (ACE2) glycoprotein receptor, which binds with the S1 domain of the SARS-CoV S protein (Kuba et al. 2005, Prabakaran et al. 2004, Li et al. 2003). Regarding the new coronavirus, studies show that SARS-CoV-2 has a greater capacity to spread in the population. This advantage seems to be conferred due to the high affinity of the spike protein (RBD portion) to its human ACE2 receptor (Wan et al. 2020). Thus, this high-affinity binding allows rapid infection of the population

through the airways and mucous membranes, through direct contact or by contact with saliva or contaminated surfaces. After infection of the initial cells, the viruses use protein S to mediate cell-cell fusion in order to infect neighboring cells, giving rise to multinucleated giant cells. Thus, the virus is able to spread in the infected organism without being detected or neutralized by specific antibodies (Hwang et al. 2006, Letko et al. 2020).

CLINICAL ASPECTS, ILLNESS EVOLUTION AND DEATHS

COVID-19 replicates efficiently in the upper respiratory tract and appears to cause common colds in the winter season (Heymann & Shindo 2020). So, symptoms like fever, cough, fatigue, dyspnea, and headache can be present in both common and severe forms (Tian et al. 2020). Laboratory studies also can show leucopenia (Li et al. 2020). The severe form may present a clinical picture ranging from shortness of breath, paroxysmal cough, and productive sputum to multifocal nodular and peripheral ground-glass opacities involving the lung lobes (Kong & Agarwal 2020). Unfortunately, it seems that hematological and biochemical exams do not show significant changes and can not use alone as diagnosis tools (Ming-Yen et al. 2020).

Zhou et al. (2020) analyzing 191 patients who tested positive for SARS-Cov-2 in two Wuhan hospitals, found a death rate of around 28.27% (n=54) in hospitalized patients. According to these authors, factors such as age, lymphopenia, leukocytosis, and altered levels of biochemical and immunological biomarkers, are associated with the severity of illness and death. However, they also related that severe lymphopenia was common in patients who died. As previously mentioned, these findings are similar to the

study published by Tan et al. (2020), which showed lymphopenia in 5 patients who died.

BRAZILIAN ILLNESS EVOLUTION

The first case in Brazil occurred in February 26th, in São Paulo state. A man, 61 years old, arrived from Italy and presented the characteristic symptoms of the disease. Two days later, around 182 suspect cases occurred in 16 Brazilian states. The initial recommendations from the Brazilian Ministry of Health were based on WHO instructions to prevent contagion of the virus in the population are shown in Figure 3. After the flowchart adoption for health professionals, the evaluation criteria was changed, and new statistic data started to be published daily (Brazil 2020a). From April, the contagion was widely distributed and it was difficult to detect the virus propagation area and control the virus spread in Brazil.

Although in March 18th those criteria were published by the Brazilian government, the current instructions were modified since the confirmed cases started to be originated through community transmission. Thus, only serious cases associated with hospitalization or quarantine reclusion have been tested with specific kits (RT-PCR investigation and the ELISA kit). In this sense, asymptomatic, light and moderate cases were not investigated and notified from February to April. The last Brazilian panorama to date shows the increase of cases in May 30th, with 514,849 confirmed cases and 29,314 deaths. From this date, Brazil such as Russia, United Kingdom, and the United States, trespass the Chinese numbers, and the prevision to the next two months (June and July) has been tough for the population. The evolution of cases can be seen in Figure 4, and Figure 5 shows the numbers of Brazilian cases by state (Brazil 2020a).

The initial structure for the care of COVID-19 suspected patients or patients who presented moderate symptoms of the disease is the Family Health Unit, which consists of a public health network (Brazilian Unique Health System) with clinics, ambulatory and hospitals, located in different neighborhoods of the country's cities. On the other hand, patients who can pay for the health service (Brazilian Supplementary Health), use private clinics, ambulatory and hospitals. In addition, the major recommendation for the population is that health units should only hospitalize patients who have severe symptoms of the disease. In this way, a telephone service center was created to answer questions about the symptoms in order to guide the population to those should or should not seek hospital care. In this way, according to the clinical situation of each patient, hospitalization could be indicated for the ICU or ward beds. Until May 2020, there were 64 reference hospitals distributed in all five Brazilian regions, 25 in the North, 15 in the Northeast, 4 in the Midwest, 5 in the Southeast, and 15 in the Southern region. Those hospitals were chosen because they have ample capacity to serve the population, with specialized professionals in risk situations for public health. Moreover, also until May, another 304 hospitals across Brazil were in the verification process, in order to become reference centers in COVID-19 mitigation phase. Data from April showed that more than twenty field hospitals were built in the country (Brazil 2020b, c).

ECONOMIC ASPECTS OF THE COVID-19 PANDEMIC IN BRAZIL

COVID-19 has shown huge economic downfalls and a severe impact on public health worldwide. Financial markets fell on different stock exchanges. Official data from Economy

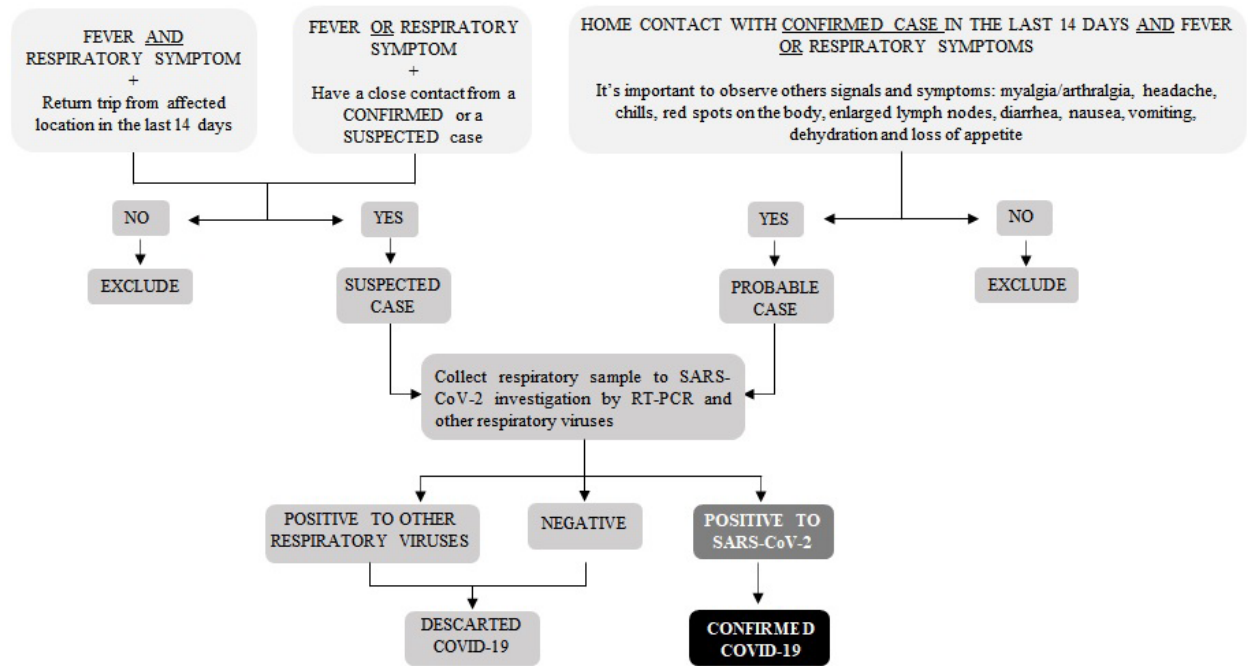


Figure 3. Flowchart with initial recommendations of the Brazilian Ministry of Health to the investigation of new cases by health professionals and sanitary vigilance (Brazilian Ministry of Health site, March 18th).

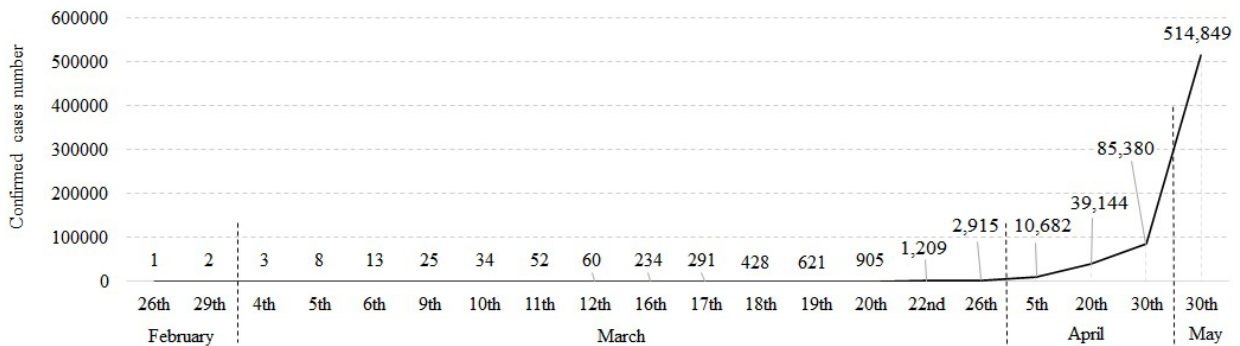


Figure 4. Infographic showing the evolution of the cases in Brazil. All numbers are associated with confirmed cases through the PCR test. The last data was recovered from the Brazilian Ministry of Health in May 30th which also computed 29,314 deaths by COVID-19.

Ministry (2020) shows that from March 9th to 13th, São Paulo stock market accumulated a drop of just over 15%. It is the worst weekly drop since October 2008 financial crisis (De Barros & Santos 2019, Rodrigues & Clemente 2019). In March 16th, financial markets fell on the world’s major indices. As a result, the circuit breaker mechanism, in São Paulo and New York cities,

temporarily paralyzed the trading session in attempt to decelerate the pace of falling stocks. In this context, the Brazilian government has taken action to try to mitigate the increasing effects of the pandemic on the economy.

The government’s first reaction, after the beginning of COVID-19 in Brazil was to reinforce the need to approve reforms that alleviate

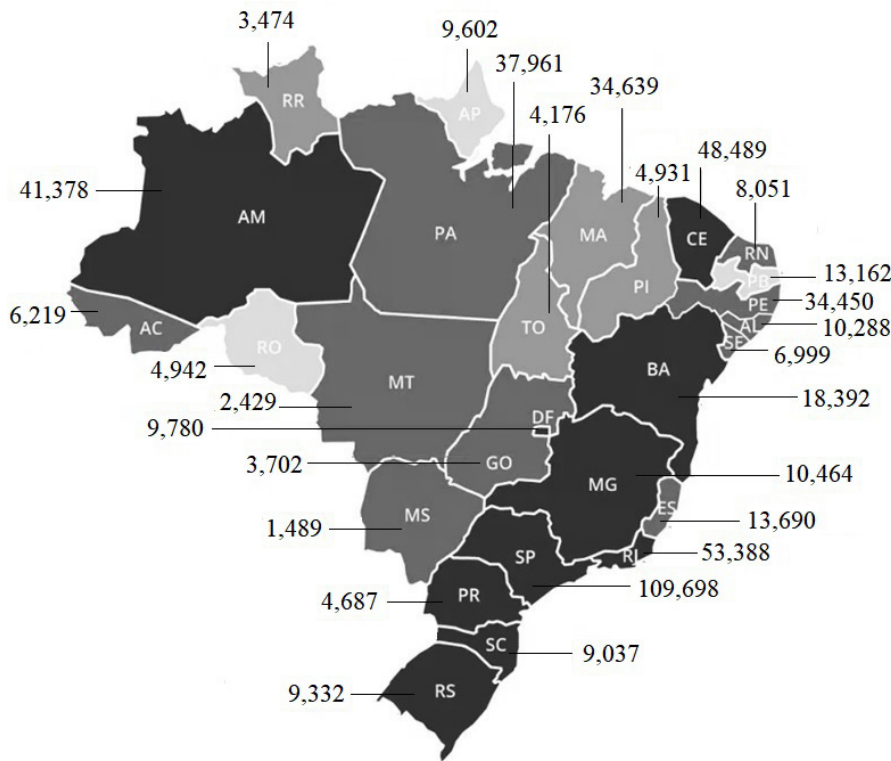


Figure 5. Total cases investigated in Brazil according to Ministry of Health (May 30th, 6 p.m. Brazilia time). Map adapted using data from State Health Secretaries of Brazil.

government spending, such as balancing public accounts in order to create an improvement in the Brazilian business environment. This action would increase investor confidence and the possibility of investing money in the country. Brazilian economic team released US\$ 29,1 billions, which would be distributed to support the economy in several Brazilian sectors. Exclusive financial support to public health was around US\$ 1 billion, of which 94.11% (US\$ 948 millions) was under Ministry of Brazilian Health control and 5.89% (US\$ 590 thousands) were released directly to the Federal University Hospitals, linked to the Ministry of Brazilian Education. Moreover, in March 16th, the Brazilian economic team announced the release of more than US\$ 890 millions to the Unified Public Health System, from the Mandatory Insurance for Personal Damage Caused by Motor Vehicles by Land that remains available in public coffers. Imported medical products also experienced a

decrease in import taxes until the end of 2020. The last financial support (from US\$ 120 to US\$ 240), for poor people and in risk situation, also named informal or autonomous workers was distributed in April. Table I shows other government actions, to support companies and consumers (Brazil 2020d, e).

Brazil adopted drastic measures to block the virus advance. In March 18th, São Paulo was the most affected state in Brazil. The government determined the closure of malls, fitness centers, stores and offices that operated within the metropolitan region of the city until April 5th (Brazil 2020f, g). Likewise, the government of Pernambuco, in March 19th, announced the closure of malls, beauty salons, restaurants and coffee shops across the state (Brazil 2020h). Thus, these measures were adopted by several other states in Brazil, such as Bahia (Brazil 2020i), Ceará (Brazil 2020j), Rio de Janeiro (Brazil 2020k), and Santa Catarina (Brazil 2020l). The

Table I. Brazilian government actions adopted to mitigate the increasing effects of the COVID-19 pandemic on the country economy.

Target-public	Actions
Retirees and pensioners from the National Social Security Institute	The half part of the 13 th salary was brought forward to April and the other half, anticipated for May, totaling US\$ 9 billions in these two months.
Companies	Public banks, such as Caixa Econômica Federal, provide around US\$ 14.8 billions to working capital for companies, of which 53.33% (US\$ 7.9 billions) of this amount destined to the working capital of companies and the remaining 46.67% (US\$ 6.9 billions), used to buy credit lines from small and medium-sized companies.
Formal workers	Around US\$ 21.5 billions was released to the Severance Pay Fund, with the salary bonus anticipated to June, generating another US\$ 2.5 billions for the Brazilian economy.
Low-income population	Bolsa Família social program was expanded, receiving the support of the US\$ 610 thousands. The expectation is that more than 1 million beneficiaries will be attended.
Tourism sector	Working capital loans was created. Resulting in a rescue action for airlines, which suffer from the drop-in demand for services. Moreover, to stop the crisis in the civil construction sector, the government evaluates to release US\$ 14.8 billions to boost the services.
Informal workers	A value between US\$ 120 and 240 was granted for three months.

Senate also unanimously approved, in its first remote deliberative session, a legislative decree, which recognizes the state of public calamity in the country due to the COVID-19 pandemic. The government could be able to breach until December 31st in the current year the fiscal target, and it could release even more resources to fight the pandemic. The instructions until April 20th, indicated that all social isolation measures and commerce closure would be extended until May. Thus, all people in all states should stay in their homes and in some cases possible taxes could be applied.

CHINA'S TEACHINGS AND PROSPECTS FOR THE MANUFACTURE OF IMMUNOBIOLOGICALS

Chinese discovered the virus and sequenced its entire genome a week later from the first

identified case. Compared with other cases, such as SARS sequencing in 2003 that lasted months or HIV that lasted years, sequencing SARS-CoV-2 had a quick and effective response (Lu et al. 2020). Obtaining the virus genome was essential to start developing test kits for diagnosis, vaccines strategies, and other treatments (Prompetchara et al. 2020, Shanker et al. 2020).

China also showed that the clinical features of the first 41 patients in Wuhan who tested positive for SARS-CoV-2 symptoms included diseases of the lower respiratory tract, fever, dry cough, and dyspnea (Huang et al. 2020). Such manifestations are similar to those diseases caused by other Coronaviridae family representants that cause Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome (MERS) (Zaki et al. 2012, De Groot et al. 2013). The vast majority of patients after the third day of symptoms

showed abnormal characteristics on computed tomography (CT), such as focal ground-glass opacity associated with smooth interlobular and intralobular septal thickening in the right lower lobes and also, a small amount of pleural effusion in some cases (Li et al. 2020, Wu et al. 2020). However, different radiological patterns were observed at several times through the course of the disease. For example, the time between the onset of symptoms and the development of acute respiratory distress syndrome (ARDS) was around nine days among patients with COVID-19 pneumonia. These findings confirm the importance of early recognition of the disease is essential for the clinical cure of patients (Zhao et al. 2003, Xu et al. 2020a).

When a new outbreak begins, the primary strategy is specific, reliable, accurate, and detect methods for tracking infected and uninfected people (Ai et al. 2020). In the early days of the outbreak in Wuhan, the health system had no test available kits and the screening depended on the laboratory analysis of the nucleic acid sequencing of the virus, which is time-consuming. Thus, second related by China's Government, China's National Medical Products Administration took steps to accelerate the work of biotechnology companies to develop detection kits. Therefore, in January 13th, the first kit was released, with enough supplies available just for two weeks. Independent of speculative information about possible China's Government omission or non-revelation of the true face of its cases, the Chinese experience taught and reinforced to the world the importance of listening to experts in science and public health and made it clear how Chinese people are essential to global health (Anderson et al. 2020, WHO 2020).

The systematic and proactive organization of Chinese risks, based on collaboration between government, health experts and WHO,

has helped the world during the pandemic through the release of disease-related clinical data (Chinazzi et al. 2020, Xu et al. 2020b). Data of more than 40.000 cases in China could shown that 80% of patients infected with COVID-19 did not need medical intervention (asymptomatic), while the other 20% needed treatment in hospitals.

The obtention of immunobiological tools for the infection is associated with insights learned from the outbreak of SARS-CoV and MERS-CoV (Prompetchara et al. 2020). As previously mentioned, the immunological findings to date are too preliminary to draw definitive conclusions. Zhou et al. (2020), investigating 99 cases, showed an increase in total neutrophils (38%), a reduction in total lymphocytes (35%), and an increase of serum IL-6 (52%) and C-reactive protein (84%). These results were reinforced by Tan et al. (2020) and Huang et al. (2020), observing the patients who needed ICU care due to COVID-19, showed the increase of the different cytokines such as IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, and TNF- α . It has also been reported that SARS-CoV directly infects macrophages and T cells, and have a weak antibody response (Perlman & Dandekar 2005). Finally, Prompetchara et al. (2020) indicated that COVID-19 can induce a "cytokine storm" which can initiate viral sepsis and inflammatory-induced lung injury. Moreover, it can lead to other complications, including pneumonitis, acute respiratory distress syndrome (ARDS), respiratory failure, shock, organ failure, and potentially death.

Thus, SARS-CoV immune response (in severe disease) is associated with strong T cell responses, higher titers of neutralizing antibody, and more serum Th2 cytokines (IL-4, IL-5, IL-10) (Li et al. 2008, Prompetchara et al. 2020). Likewise, in MERS-CoV infection, the early increase of CD8⁺ T cells correlates with

disease severity, and at the convalescent phase, dominant Th1 type helper T cells are observed (Shin et al. 2019, Prompetchara et al. 2020). Regarding the humoral response, according to Thevarajan et al. (2020), both immunoglobulin M (IgM) and immunoglobulin G (IgG) are antibodies that bind to the SARS-CoV-2 and they were detected in human blood before symptomatic recovery. These immunological changes persisted for at least 7 days following full resolution of symptoms. Briefly, if the Th1 response appears to be the key to the successful control of SARS-CoV and MERS-CoV, it is likely to be true also for SARS-CoV-2. The enhance of this Th1 response is a feasible way to make an efficient vaccine.

Data from May 2020 showed that more than 120 vaccines have been developed around the world and eight of them already in clinical trials. Specifically in Brazil, researchers from the Immunology Laboratory of the Heart Institute (Medicine Faculty of the São Paulo University) have developed a vaccine based on Virus-Like Particles (VLP). The group of Biotecnology Research Centre (CTVacinas) formed by researchers from Federal University of Minas Gerais, René Rachou Institute and Hearth Institute of São Paulo has developed an attenuated-virus vaccine, based in H1N1 virus inoculated with genetic information of SARS-CoV-2 (Brazil 2020m,n).

COMPARISON WITH THE MOST AFFECTED COUNTRIES NUMBERS

Although we have learned more about the biology of SARS-CoV-2 infection and the consequent development of COVID-2019, a vaccine should only be available to the population within 10 to 18 months (in the best scenery). Regarding the treatment of COVID-2019, the development

of new drugs seems to be less feasible—due to the time required for their development, testing, approval, and large-scale production. Thus, there is a great effort to evaluate the effectiveness of existing drugs approved for use in other diseases, for the treatment of individuals with COVID-2019. In this sense, there are encouraging results, but nothing conclusive to date.

Brazil, like many other European countries and even the USA, took long to implement preventive measures regarding the entry of SARS-CoV-2 in its territory. Even after confirmation, it seems to have had a delay in the beginning of the social isolation. Brazil has currently gone through the exponential phase of the COVID-19 cases (514,849 confirmed cases and 29,314 deaths in May 30th). Until April, Brazil had a number of cases similar to those in Italy at the beginning of the outbreak. Italy adopted quarantine measures when 7,375 cases and 366 deaths had already been registered in the country (Figure 6). It was observed that countries had their epidemic times started when they had at least 100 cases each (it was considered the 1st day). Figure 6 also shows that as earlier the quarantine begins as slower the progress of the cases. Spain, Italy, France, and the United States initiated social isolation when there were already 6391 (13th day), 7375 (15th day), 7730 (18th day), and 43781 (22nd day) cases, respectively.

PRELIMINARY CONCLUSIONS AND FUTURE PERSPECTIVES

The collapse of the health system in Brazil was not different from the world scenery. Data obtained on May 30th (Table II) shows the hard reality of the country and could help some states and municipals in the adoption of new strategies. However, the pressure of the economy,

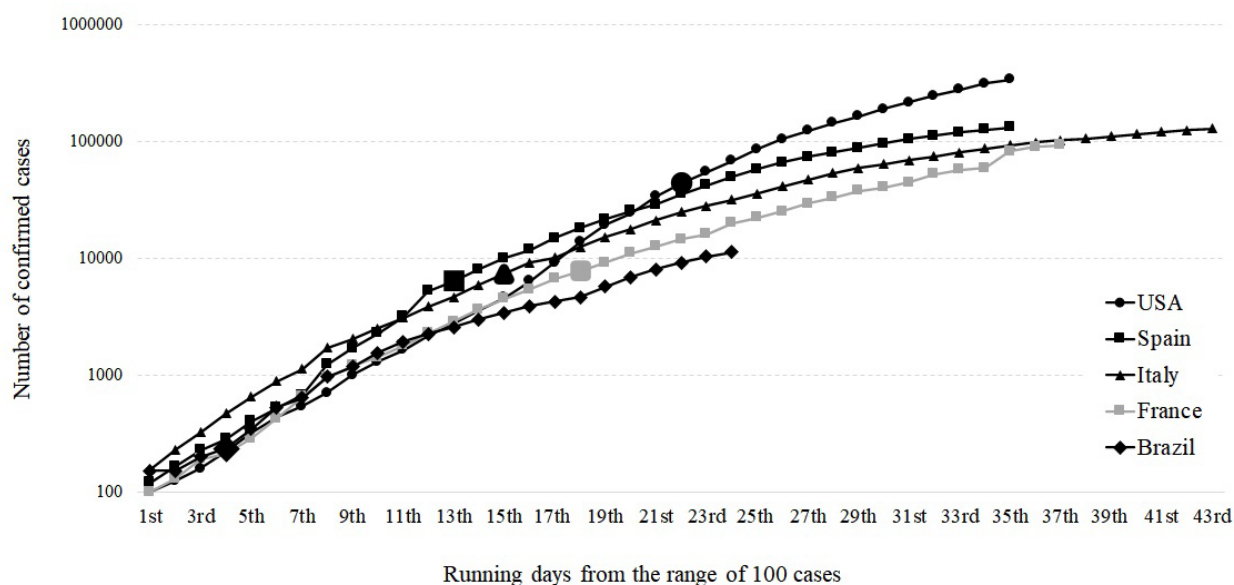


Figure 6. Graphic shows the relationship between the speed of the exponential increase in cases of COVID-19 between countries and the beginning of the adoption of social isolation measures (points highlighted). Source: <https://www.worldometers.info/coronavirus/>.

companies, and employers led governors and mayors to the flexibility of the quarantine from June. In this sense, the future of contagion is uncertain.

Although many incentives were adopted to face the disease, great part of the population did not adhere to the social isolation or used a Personal Protective Equipment (PPE) in public places. Brazilian media has argued that possibly it's due to the Brazilian president's behavior, speech, and actions. The Brazilian president showed up himself in Brazilian media, without using PPE in public places, disrespecting the social isolation measures imposed by the state governors. In addition, the president has posted in his personal social media different opinions against OMS recommendations.

The Brazilian behavior gained international notoriety and The Lancet Journal (May 9th, 2020) showed a repudiation note in response to him. According to the Journal the Brazilian President "not only continues to sow confusion by

openly flouting and discouraging the sensible measures of physical distancing and lockdown brought in by state governors and city mayors but has also lost two important and influential ministers in the past 3 weeks" (Lancet 2020).

The social financial support, to informal workers and poor people promoted daily extensive bank rows increasing the virus exposition. In addition, several of health professionals have gotten sick promoting a decrease in the hospital's attending.

Epidemiology experts from the Brazilian Ministry of Health initially indicated that the peak of the infection could occur in April, with the plateau expectation in May/June, remaining until July and decreasing in August/September. Recent data shows that the probable peak will be in June/July, remaining until August and without decreasing prevision.

Up to the end of this manuscript written (June 7th), the curve of confirmed cases had been increased and health services like reference hospitals and field hospitals, in

Table II. Estimative of occupied hospital beds in May 30th, 2020 in Brazilian public hospitals. Data were found in the Health Secretaries sites of each state at the above date.

Brazilian state	Occupied hospital beds (%)
Pernambuco	98.00
Amapá	97.98
Maranhão	97.50
Rio Grande do Norte	93.00
Sergipe	89.60
Ceará	89.00
Rio de Janeiro	86.00
Pará	84.36
Acre	78.20
Alagoas	78.00
Espírito Santo	77.55
Paraíba	73.00
Rio Grande do Sul	72.00
Amazonas	71.00
Minas Gerais	70.00
São Paulo	69.30
Bahia	68.00
Goiás	66.15
Rondônia	62.00
Piauí	61.00
Santa Catarina	59.10
Tocantins	50.00
Paraná	44.00
Distrito Federal	42.24
Mato Grosso	14.60
Mato Grosso do Sul	02.80
Roraima	Data not found

different states of the country, showed only 10% of the total capacity to attend the patients with COVID-19. The perspective of some sanitary authorities up to the end of the first semester of 2020 is the collapse of hospitals, morgues, and cemeteries, and many sick and depressed health professionals. However, with the science advance is possible to find anytime a new drug, combined treatments, and efficient immunotherapies to change this panorama until the vaccine discovery.

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