Covid-19 research with humans in Brazil

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Abstract

The Covid-19 pandemic challenges research institutions with the urgent need of responding to the morbidity and mortality caused by the virus. This study aimed to overview studies with humans on this disease in the first three months of 2020, in Brazil. Official data of the population and research protocols on Covid-19, distributed by Brazilian states, supported this temporal analysis. The incidence of the virus has grown exponentially, especially in the North and Northeast regions. Despite the discrete, slow, and asymmetric diffusion of studies, they are concentrated in the Southeast, and few clinical trials have entered Phase II. The geographical distribution of research ethics committees, higher education institutions, investments in science and technology, health centers and hospitals generate state vulnerabilities when addressing the disease. Close longitudinal follow-up should be carried out in the face of regional inequities, to defend bioethical principles and human life.
Keywords: Coronavirus. Sars virus. Bioethics. Human experimentation. Clinical trial.

Resumo

Panorama de pesquisas com seres humanos sobre covid-19 no Brasil

A pandemia de covid-19 desafia instituições de pesquisa pela urgência de responder à morbimortalidade provocada pelo vírus. O objetivo deste estudo foi traçar panorama das pesquisas com humanos sobre essa doença no primeiro trimestre de 2020 no Brasil. Dados oficiais de saúde da população e de protocolos de pesquisa sobre a covid-19, distribuídos por estados brasileiros, subsidiaram a análise temporal. Houve crescimento exponencial da incidência do vírus, principalmente nas regiões Norte e Nordeste, apesar da difusão discreta, lenta e assimétrica das pesquisas, concentradas no Sudeste. Os poucos ensaios clínicos entraram na Fase II. A distribuição geográfica de comitês de ética em pesquisa, instituições de ensino superior, investimentos em ciência e tecnologia e unidades assistenciais básicas e hospitalares gera vulnerabilidades estaduais para enfrentar a doença. Acompanhamento longitudinal atento deve ser realizado diante das iniquidades regionais, em defesa dos preceitos bioéticos e da vida humana.
Palavras-chave: Coronavírus. Vírus da Sars. Bioética. Experimentação humana. Ensaio clínico.

Resumen

Panorama de investigaciones con seres humanos sobre covid-19 en Brasil

La pandemia de covid-19 desafía a las instituciones de investigación en la urgencia de responder a la morbilidad y mortalidad causadas por el virus. El objetivo de este estudio fue esbozar una visión general de la investigación con humanos sobre esta enfermedad en el primer trimestre de 2020 en Brasil. Los datos oficiales sobre salud, población y protocolos de investigación sobre covid-19 distribuidos por la unidad federativa brasileña respaldaron un análisis temporal. Hubo un crecimiento exponencial en la incidencia de covid-19, especialmente en las regiones del Norte y Nordeste, a pesar de la diseminación discreta, lenta y asimétrica de la investigación, concentrada en el Sudeste. Los pocos ensayos clínicos estaban en Fase II. La distribución geográfica de los comités de ética de la investigación, las instituciones de educación superior, las inversiones en ciencia y tecnología y las unidades de atención desde la red básica hasta el hospital identificaron los potenciales y vulnerabilidades estatales para hacer frente a la enfermedad. Se debe llevar a cabo un monitoreo longitudinal atento ante las desigualdades regionales, en defensa de los preceptos bioéticos y de la vida humana.
Palabras clave: Coronavirus. Virus del SRAS. Bioética. Experimentación humana. Ensayo clínico.

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With the disease caused by the novel coronavirus (Covid-19), the world faces a public health and civilizing crisis not seen since the Spanish flu of 1918, with a challenging number of contaminations even with the efforts of governments and research institutions [1]. The global geopolitical scenario in the pandemic intensifies economic and social inequalities, as well as the divergence between countries and the World Health Organization (WHO) [2,3]. The U.S. presidential demand, at the beginning of the pandemic, for a rapid Covid-19 vaccine showed discredit in the scientific stages, which require several phases and pre-clinical and clinical studies [4]. Accelerated contamination, high morbidity and mortality, and the absence of pharmacological treatment have made social distancing and biosecurity the only effective weapons against Covid-19 [5].

After three months, the political pressure in Brazil worsened with contradictory discourses on the virus impact, disdain for the high lethality rate of the disease [6,7] and the removal of epidemiological data from official websites [8]. The public repudiation note of the Brazilian Society for the Advancement of Science, the Brazilian Academy of Sciences and 70 other entities [9] and the actions of state health departments sought to maintain data transparency on alternative websites and reliability for decision-making [8]. It is important to develop an evidence base to establish better healthcare standards, new interventions, and management guidelines in public health [10].

In 2016, WHO published the *Guidance for managing ethical issues in infectious disease outbreaks* [11] to ensure scientific validity of the rights and safety of participants in studies conducted during outbreaks. The guideline emphasized the moral obligation to conduct timely research, respecting basic ethical principles of studies with human beings [12], such as autonomy, beneficence, non-maleficence and justice [13]. This principlism is essential for clinical research, and its perception must be parsimonious to avoid misunderstandings in extreme conditions [14].

Trials include supervisory processes and can be performed quickly without compromising participants' safety, and randomized clinical trials are considered ideal to support causal inference, despite their epistemic limits to address population health and analyze direct harm or benefits to participants [15].

Covid-19 studies involve multiple ethical controversies. The placebo arm of research covers individual physical risks, such as additional pain, suffering or death; in the randomization of the active treatment arm, the benefit is uncertain, and unrecognized damage may occur [10]. Thus, decisions on the prioritization of treatment accentuate discussions in the media and in public debate [16].

With limited resources in the pandemic, the collective benefit is more important than the individual, even though a patient's request for care must be respected, maintaining his autonomy. The impartial distribution of critical respiratory support care, such as mechanical ventilators, is ruled by values that are not usually considered [17]. The protection of justice is under strain, allowing Covid-19 patients with better results to be prioritized over a substantial amount of non-urgent care, which has a negative long-term effect [16].

Thus, the pandemic challenges healthcare systems with an unprecedented number of critically ill patients. Measures to minimize the gap between needs and resources depend on the reduction of viral transmission and increased treatment capacity, which can be made possible by ethical scientific studies [18]. So, this article aimed to trace an initial overview of research on Covid-19 conducted with humans during the first quarter of the pandemic, and potentially innovative factors and assistance to face the disease in Brazil, discussed in the light of current bioethical norms.

Material and methods

This is a quantitative study, with documental analysis of data from the Ministry of Health [19-24], Ministry of Education [25] and Ministry of Science, Technology and Innovations [26] available between March and May 2020, during the first three months of the Covid-19 pandemic in Brazil. Since official and secondary data are used, the bioethical principles of the National Health Council Resolution (CNS) 510/2016 [27] were adopted.

To measure in the country the impact of the disease and studies with humans in progress, research protocols and the subcategory of clinical trials approved in each state was associated with the Covid-19 incidence coefficient, obtained at different periods. The monthly public data provided by the Ministry of Health was collected from the epidemiological bulletins of the National Committee of Ethics in Research (Conep), in three periods: T1 (bulletin 1, of March 23rd, 2020 or

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13th epidemiological week)[19], T2 (bulletin 10, of April 24th, 2020 or 17th epidemiological week)[20] and T3 (bulletin 19, of May 26th, 2020 or 22nd epidemiological week)[21].

To determine the Covid-19 incidence coefficient in each state and in the country, the number of confirmed cases[22] was divided by the resident population[23] and multiplied by the population base of 100,000 inhabitants. Simple descriptive analysis was used for the absolute frequency of the number of research protocols and clinical trials approved in each state and in Brazil[19-21].

The clinical trials registered in T3[21] and detailed at *Plataforma Brasil*[24] (Brazil Platform) were categorized according to protocol title, number of participating centers and number of volunteers in Phase I (initial phase, with healthy volunteers, in tens), Phase II (pilot therapeutic study, with target population, in hundreds), Phase III (expanded therapeutic or large randomized studies, multicenter studies, with hundreds to thousands of participants) or Phase IV (post-registration study, pharmacovigilance, with thousands to millions of participants). The relative frequency of clinical trial phases was expressed as a percentage in Figure 1.

To relate this scenario to the infrastructure to fight the virus of each state, two analysis groups were formulated: Category 1, research and innovation; and category 2, research and assistance. The first counted the absolute frequency of research ethics committees (CEP) registered at *Plataforma Brasil*[24], higher education institutions active in the electronic register of the Ministry of Education[25] and the coefficient of investments in science and technology (S&T). This indicator was calculated by the amount of million *reais* invested in S&T, referring to research, development, scientific activities and related techniques, invested in the last year by the Ministry of Science, Technology and Innovations[26], divided by the resident population[23] and multiplied by the population base of 100,000 inhabitants. Category 2 recorded data released by the Ministry of Health regarding the absolute frequency of public testing laboratories[22], family health teams[23] and public reference hospitals[22]. Simple descriptive analysis was adopted for absolute data.

Results

Table 1 shows that the Covid-19 incidence coefficient increased exponentially during the first quarter of the pandemic throughout Brazil, especially in the North and Northeast regions. This was accompanied by a slight increase in the number of research protocols on the disease, and approved clinical trials corresponded to a small portion of the total in Brazil (18.4%), mostly in São Paulo.

Table 1. Covid-19 incidence coefficient, research protocols and clinical trials approved in the first trimester of the pandemic, by Brazilian state

	Covid-19 incidence coefficient*			Research protocols			Approved clinical trials		
FU	T1	T2	T3	T1	T2	T3	T1	T2	T3
RO	0.16	13.46	175.89	–	–	–	–	–	–
AC	1.27	26.19	519.26	–	1	2	–	–	1
AM	0.75	68.11	714.16	1	5	6	1	3	3
RR	0.37	54.31	459.69	–	–	–	–	–	–
PA	0.06	14.68	302.21	–	1	2	–	–	1
AP	0.12	65.01	781.10	–	–	–	–	–	–
TO	0.31	2.31	168.57	–	–	–	–	–	–
MA	0.03	24.67	319.98	–	–	–	–	–	–
PI	0.19	6.71	109.77	–	–	2	–	–	–
CE	1.78	50.10	394.24	–	1	7	–	1	1
RN	0.36	19.68	132.26	–	–	3	–	–	–
PB	0.05	8.42	195.61	–	2	5	–	–	–
PE	0.44	36.46	293.93	–	3	9	–	–	–
AL	0.20	9.47	195.40	–	1	3	–	–	–
SE	0.43	5.27	231.61	–	3	3	–	–	–
BA	0.41	11.52	91.50	–	8	18	–	–	–
MG	0.60	6.10	32.45	–	13	29	–	2	4
ES	0.70	32.93	250.44	–	–	1	–	–	–

continues...

Table 1. Continuation

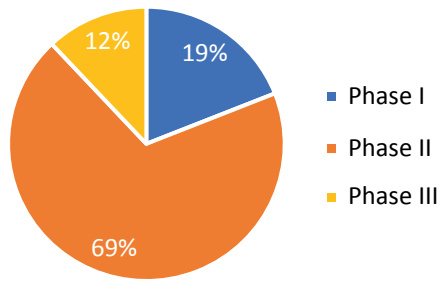
	Covid-19 incidence coefficient*			Research protocols			Approved clinical trials		
FU	T1	T2	T3	T1	T2	T3	T1	T2	T3
RJ	1.37	36.42	231.89	–	17	32	–	7	7
SP	1.62	36.34	181.54	4	89	150	1	18	32
PR	0.49	9.38	28.87	–	9	16	–	1	3
SC	0.94	15.35	94.62	–	2	5	–	–	–
RS	0.75	8.71	57.45	–	15	37	–	–	8
MS	0.75	6.64	36.53	–	1	2	–	–	–
MT	0.06	6.40	43.41	–	1	1	–	1	1
GO	0.33	6.46	35.80	–	2	4	–	–	–
DF	4.13	29.88	215.01	–	3	10	–	1	3
Brazil	0.89	23.34	176.77	5	177	347	2	34	64

**FU: Federation unit; *Population base: 100,000 inhabitants. T1=03/23/2020, T2=04/24/2020, T3=05/26/2020*
Source: Brazil [19-23].

According to Figure 1, of the 64 clinical trials approved until May 2020, 69% were in Phase II, with no authorized national research in Phase IV. It is important to highlight that a study in São Paulo was completely suspended and another study in Amazonas was partially suspended, due to a higher dose arm, after the approval of protocols.

Table 2 presents information on research with human beings related to innovation or assistance. Family health teams are fundamental for the first care of suspected Covid-19 cases, and their number exceeds that of other specialized diagnostic or treatment units in all states. The North region presented the smallest amount of family health teams, and the Southeast region the largest number of higher education institutions, research ethics committees, and investment coefficient in S&T, being an innovation center in the fight against Covid-19.

Figure 1. Covid-19 clinical trials in Brazil in the first quarter of the pandemic



Source: Brazil [21,24].

Table 2. Physical and financial resources involved in research, innovation, and assistance, by federated units and in the country

	Category 1 - Research and innovation			Category 2 - Research and assistance		
FU	Research ethics committees	Higher Education Institution	S&T investment coefficient (R$)*	Public testing laboratories	Family Health Teams	Reference public hospitals
RO	12	36	5.34 mi	1	355	2
AC	3	14	9.17 mi	1	183	1
AM	15	33	4.00 mi	1	692	6
RR	4	10	5.70 mi	1	134	2
PA	21	89	2.21 mi	2	1,494	11
AP	3	16	0.68 mi	1	180	1
TO	10	33	3.65 mi	1	519	1
MA	9	65	2.18 mi	1	2,082	2
PI	12	52	2.52 mi	1	1,297	1
CE	39	117	3.88 mi	1	2,530	1
RN	6	34	6.19 mi	1	1,018	2
PB	16	54	6.56 mi	1	1,453	2

continues...

Table 2. Continuation

FU	Category 1 - Research and innovation			Category 2 - Research and assistance		
	Research ethics committees	Higher Education Institution	S&T investment coefficient (R$)*	Public testing laboratories	Family Health Teams	Reference public hospitals
PE	32	145	3.01 mi	1	2,300	2
AL	5	36	0.88 mi	1	897	1
SE	4	26	3.63 mi	1	651	1
BA	49	179	4.13 mi	1	3,810	1
MG	96	370	5.29 mi	1	5,597	1
ES	15	85	4.35 mi	1	780	2
RJ	69	167	7.81 mi	2	2,295	1
SP	204	696	25.76 mi	1	5,241	1
PR	57	225	11.27 mi	1	2,327	7
SC	37	124	8.10 mi	1	1,825	2
RS	60	148	4.16 mi	1	1,929	2
MS	6	46	5.42 mi	1	629	1
MT	13	71	7.75 mi	1	730	1
GO	26	134	4.40 mi	1	1,541	2
DF	23	95	11.32 mi	1	454	1
Brazil	846	3,100	9.77 mi	29	42,943	58

**FU: Federation unit; *Population base: 100,000 inhabitants; S&T: science and technology*
Source: Brazil [22-26].

Discussion

Research with human beings in Brazil during the pandemic is essential to generate data on the disease and should be based on the ethical principles of CNS Resolution 466/2012 [28]. Other norms in force are continuously improving [29] and have a lot to contribute. For example, CNS Resolution 510/2016 [27] for humanities research, CNS Resolution 553/2017 [30], addressing patients' rights and duties, and CNS *Carta Circular* 166/2018 [31], with a code of conducts for case reports. In addition, CNS Resolution 580/2018 [32] discusses research of strategic interest to the Unified Health System (SUS) and CNS Resolution 588/2018 [33] presents the National Health Surveillance Policy.

The maximum representations of autonomy in clinical studies are the informed consent form and the consent form – a similar document for minors or legally incapable people [28]. In times of social isolation, a major strategy for mitigating Covid-19 in the Brazilian territory [34], obtaining physical signature from participants becomes more difficult, but even surveys with remote data collection must electronically attest their approval or justify their absence, in the case of secondary data [35,36].

Non-maleficence is the idea of not exposing individuals to harm. This reinforces the necessary caution in clinical and Phase II studies, which are still scarce in Brazil, unlike places with a higher history of outbreaks, such as China, where intervention research prevails [12]. So far, no pharmacological risk-free agent has been approved at all stages for treating the virus, but fatal adverse effects have been reported in patients using test drugs [37-40]. Even so, the Brazilian Ministry of Health allowed the use of hydroxychloroquine and chloroquine for critically ill patients [41].

The controversy extended to the international scientific sphere, as a study published in *The Lancet* [42] mistakenly concluded that these drugs were effective. However, the own editors of the journal [43] and 120 scientists [44] from 26 countries – mostly Asian, European and African, a few from Oceania and the Americas, and none from Brazil – spoke out against the false results of the article. Thirteen days after publication, the authors of the article apologized [45], showing that this period of intense global academic debate on the reliability and repercussion of research is important for protecting participants.

The incidence coefficient presented in this study refutes the pandemic denial [46], proving it is a serious public health issue, and that clinical research can assist the population directly or indirectly [28]. But the lack of clear benefits in research protocols on the disease can create conflicts when risks are high, as observed in China in proposals for the use

of Interferon Alfa and traditional medicine, or when the level of biosafety is inadequate [12].

Main decisions based on clinical trials should be entrusted to physicians and experienced teams, who will apply all available resources [2]. In the pandemic, given the high risk of contamination, individual rights of hospitalized patients with Covid-19 are limited, as well as funeral arrangements or necropsy. These measures should be understood as exceptional conditions [47], and new research on the efficacy of medicines, personal protective and supportive equipment can justify practical changes that benefit patients [28,30,32,33].

We emphasize the timid advance of research protocols in Brazil and the importance of continuous investments in S&T, since the scarcity of resources can cause difficult decisions related to beneficence and non-maleficence [16]. The asymmetric distributions of investments, research centers, and assistance verified in this study are inequities in the fight against Covid-19 in Brazil. The country has become one of the epicenters of the disease, whose geographical distribution is marked by interiorization [5], with metropolitan regions spreading the virus to poorer cities in the countryside [48].

The North region was affected later, but the incidence of Covid-19 was high and alarming, with higher risk of healthcare collapse [34,48], which corroborates the findings of this study. Access to different SUS services is a universal and integral right of patients [30] and it must be preserved, regardless of personal decisions to participate in research [32]. Protocols of public health emergencies or with territories or people in situations of great risk or vulnerability [33] require special and urgent analysis, primarily aiming to reduce social and health inequalities [32,33].

Budget forecasting is an important item in care surveys in SUS [32] and health surveillance [33], which legitimizes the discussion about resource sustainability for the well-being of the Brazilian population. Covid-19 creates extremely difficult dilemmas for health professionals, and no isolated algorithm can give complete guidance or relieve the medical burden of individual evaluation, which must weigh between beneficence and justice in particular situations [49].

The recognition of ethical appreciation in public health emergencies generates greater articulation between research institutions, health systems and the community, to prioritize research that improves the well-being and reduces mortality in the short term, especially in contexts of overcrowded hospitals [2,49].

The speed of the evaluation of research on Covid-19 may be positive, as verified by ethics committees in China, where monthly collegiate meetings became almost daily, and decisions began to be released in 2.13 days, on average, with 1.81 more days in case of new submissions during the pandemic [12]. This pattern is much more dynamic than in Brazil, where the average CEP deadline for decisions is 30 days and for Conep is 60 days [29].

A multinational study involving Germany, Italy, Spain, France, the United Kingdom, Belgium, the Netherlands, Austria, Denmark, and Sweden showed that each of these countries receives more than 200 clinical trials of drugs per year, mainly in Phase III [50]. The fluctuations over the years were attributed to political influences and commercial sponsorship in Western Europe, with a 4% decrease in proposals between 2007 and 2011, stagnation between 2012 and 2013, and an 10% increase between 2014 and 2015 [50]. In Switzerland, randomized clinical trials cost, on average, US$ 72,000, with different approval intervals when comparing research ethics committees (from 82 to 92 days) and the Swissmedic regulatory agency (27 to 49 days) [36].

In Brazil, these trials depend heavily on the infrastructure of participating centers, and multicentric participation is recommended for lower costs. To develop a new drug, a dossier of clinical development is analyzed in parallel by the CEP/Conep system and regulatory bodies of the National Health Surveillance Agency (Anvisa). Only after the approval of both, the study can begin.

The Anvisa manifestation period varies from 180 days for Phases I or II, or 90 days for the others. Time is relevant in these studies, but it is necessary to consider the safety of volunteers, to guard good research practices [29]. These considerations impact national research on Covid-19, which mostly test chloroquine and hydroxychloroquine, in addition to other therapeutic forms, such as the association with azithromycin, lopinavir/ritonavir, nitazoxanide, eculizumab, tocilizumab, sarilumab, ivermectin, convalescent plasma and mesenchymal stem cells [21].

Suspensions of ongoing trials in Brazil, even in a sample universe that is still small and recent, reinforce the ethics debate during the studies. The "Brazilian way," a cultural construct used as a strategy to solve problems, cannot overlook scientific criteria and the commitment to research quality in the country [51].

In this sense, cunning or *métis*, which refers to ancient Greek thought, arises in the encounter with new challenges, and its flexible psychodynamics reminds us that new operational tactics are always present in human production, but should not disqualify or subvert the quality of knowledge [52]. Considering the immediate search for results during the pandemic, the researcher's role in protecting patients and volunteers against significant risks or damages should be recognized. If damages occur, they should be communicated to research ethics committees for the readjustment or suspension of the study [28].

The limitation of this study is related to the short time interval analyzed, the first trimester of the 2020 pandemic. However, the initial panorama of research with human beings and the dimensioning of S&T resources in Brazil contribute to decision-making in the fight against the disease.

Final considerations

Despite the exponential growth of Covid-19, initial research with humans in Brazil had a discrete, slow, and asymmetric diffusion in the states, with most clinical trials in Phase II. The geographical distribution of resources and assistance generates advances and vulnerabilities in coping with the disease. Close longitudinal follow-up should be carried out in the face of regional inequities, to defend bioethical principles and human life.

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Igor Iuco Castro-Silva conceived the study and, with Jacques Antonio Cavalcante Maciel, collected and analyzed the data, wrote and revised the article.

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