Quali-quantitative synthesis between clinical trials and patents on Covid-19 associated with CRISPR

Síntese quali-quantitativa entre ensaios clínicos e patentes de Covid-19 associados ao CRISPR

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ABSTRACT
Introduction: The work presents a comparative analysis between clinical trials and patent families on COVID-19 associated with CRISPR-Cas, ACE2 and Spike worldwide. Methods: From a total of 7815 clinical trials dedicated to COVID-19, 238 clinical trials related to CRISPR-Cas, ACE2 and Spike were identified, and 112 patent families. For the recovery of clinical trials and patent families, the ICTRP® platform of the World Health Organization, the ORBIT INTELLIGENCE® system from Questel® and the INPI COVID-19 Observatory were used, respectively. Results: Through quantitative and qualitative analysis and synthesis, a pattern of insignificant similarity was observed between the institutions that sponsor clinical trials and holders of patent families, among other correlated indicators. Conclusions: In summary, it is suggested that new public policies be created to encourage synergy between clinical trials and patents, both national, in order to induce a safe path to technological independence and, consequently, better performance in combating COVID-19 associated with CRISPR-Cas, ACE2 and Spike in Brazil.

Keywords: ACE2, clinical trial, Covid-19, CRISPR-Cas, patent, spike.

RESUMO
Introdução: O trabalho apresenta uma análise comparativa entre ensaios clínicos e famílias de patentes sobre COVID-19 associado a CRISPR-Cas, ACE2 e Spike em todo o mundo. Metodologia: De um total de 7.815 ensaios clínicos dedicados ao COVID-19, foram identificados 238 ensaios clínicos relacionados a CRISPR-Cas, ACE2 e Spike e 112 famílias de patentes. Para a recuperação de ensaios clínicos e famílias de patentes foram utilizados, respectivamente, a plataforma ICTRP® da Organização Mundial da Saúde, o sistema ORBIT INTELLIGENCE® da Questel® e o Observatório COVID-19 do INPI. Resultados: Por meio de análises e sínteses quantitativas e qualitativas, observou-se um padrão de similaridade insignificante entre as instituições patrocinadoras de ensaios clínicos e detentoras de famílias de patentes, entre outros indicadores correlacionados. Conclusões: Em síntese, sugere-se que novas políticas públicas sejam criadas para incentivar a sinergia entre ensaios clínicos e patentes, ambas nacionais, a fim de induzir um caminho seguro para a independência tecnológica e, consequentemente, melhor desempenho no combate ao COVID-19 associado ao CRISPR-Cas, ACE2 e Spike no Brasil.

Palavras-chave: ACE2, ensaio clínico, Covid-19, CRISPR-Cas, patente, spike.

1 INTRODUCTION

The system formed by the Clustered Regularly Interspaced Short Palindromic Repeat (CRISPR) and its associated protein CRISPR associated protein-9 (Cas9) is capable of editing multiple gene targets simultaneously, however, there are no robust studies on the application of this technology in human beings. In fact, it is a widely used strategy for *in vitro* studies, with important potential for in vivo applicability. However, its use includes relevant ethical limitations with significant complexity for each and every analysis case.

There are several comorbidities associated with severe COVID-19, including cardiovascular disease, one of the leading causes associated with death in infected[1], pulmonary

hypertension, chronic obstructive pulmonary disease, diabetes, lung cancer, chronic kidney disease, asthma, and autoimmune diseases. ACE2, a membrane protein, has been associated with these comorbidities[2]. However, it also plays a crucial role in the conversion of angiotensin-2, which in turn helps to control blood pressure. Thus, reducing or inhibiting ACE2 function can result in serious consequences for patients. The catalytic site and the SARS-CoV-2 binding site are located in different portions of the membrane-bound enzyme, leading to a possible intervention to reduce the affinity between ACE2 and incoming SARS-CoV-2 infectious particles and still preserving the enzyme catalytic site function. In this context, a CRISPR-Cas9-based system was designed to destabilize the SARS-CoV2: ACE2 interaction (aminoacids Phe28, Lys31 e Tyr41 located at the ACE2 the N-terminal alpha-helix). At the same time, this strategy aims to preserve the overall enzyme structural conformation by maintaining critical residues necessary for the function of ACE2[3].

In addition, the first diagnostic kit available in the world and based on the CRISPR technology was developed for COVID-19 by *Mammoth Biosciences*[4], USA and the University of California San Francisco. Notably, the diagnostic kit is a simple test, based on strips, that is easy to use and allows for rapid detection without the need to transport samples through long distances[5]. Its use was authorized by the FDA (Food and Drug Administration) for emergency use in the United States[6].

It is worth mentioning that other technique to detect SARS-CoV-2 was developed based on the CRISPR-Cas12 (another class of endonuclease), and utilizes RNA extracted from the respiratory tract. This method used artificial references and/or patients' clinical samples from the United States; results can be immediately provided to the Center of Disease Control (CDC), with predictive assent[7]. This test has also been authorized by the FDA for emergency use in the USA[8].

To diagnose COVID-19 is a challenge for the entire world. The main reasons for this are: 1) the biological material to be collected: naso and/or oropharyngeal swabs, plasma, serum or total blood; 2) the definition of a biological marker with greater chances to be detected; 3) the methodology type that was employed (virological methods, molecular biology and immunoassays); 4) the best timing during the infection to collect sample and the ideal type of sample; and 5) the accuracy of the available diagnostics methodologies. In addition, Brazil depends on multiple imported materials, mainly due to the limited number of local companies that can provide supplies for this end[9].

In Brazil (see scenario of hospitalizations in Supplementary Material[1], there are many promising initiatives in the diagnostics test field for COVID-19, which are led by renowed institutions, namely: Laboratório de Nanobiotecnologia do Instituto Nacional de Ciência e Tecnologia Teranóstica e Nanobiotecnologia (INTC TeraNano) from the Universidade Federal de Uberlândia (UFU), the Instituto Nacional de Ciência e Tecnologia em Dengue e Interação Microorganismo Hospedeiro (INTC Dengue) from the Universidade Federal de Minas Gerais (UFMG), the Centro de Biotecnologia da Amazônia (CBA) in Manaus[10], the Centro de Estudos do Genoma Humano e de Células-Tronco (CEGH-CEL) in São Paulo, the Laboratório de Genômica Mendelics in São Paulo and researchers from the Universidade Federal de Goiás (UFG) are all developing diagnostic kits for the detection of COVID-19[11].

As a rule, the literature normally addresses only articles and patents. A differential of this work lies in the panoramic approach, in which several aspects or dimensions are considered in the prospection of COVID-19. Despite the potential informational entropies, mainly for patent documents in which applicants use the most diverse linguistic techniques to hide or make access difficult for third parties, in practice it is observed that the chances of significant errors occurring with various search strands in depth intermediate are smaller than if only one branch or dimension of prospecting with a lot of depth was adopted. Thus, the focus of the query is transferred, taking the focus to the results and applicability.

Therefore, the relevance and justification of carrying out scientific, technological[12] and clinical[13] prospecting studies (and the combination between both), are of singular importance in the sense of privileging hermeneutics and the synergy of future studies, as significantly realistic and guiding foundations for building public health policies with accuracy, efficiency and effectiveness that are relevant and impactful. It is also possible to infer that the theoretical framework confirmed the hypothesis that there are correlations[12] between the institutions sponsoring clinical trials and the institutions holding patents, worldwide.

In this study, we present a comparative analysis between clinical trials and patent families on COVID-19 associated with CRISPR-Cas, ACE2 and Spike worldwide.

2 METHODOLOGY

The study methodology was performed according to the following steps hereafter described.

[1] https://bit.ly/3YOf8Dr

2.1 PRE-PROSPECTION

Initially, research was carried out in the International Patent Classification (IPC) and in the Cooperative Patent Classification (CPC). Among the data obtained, nine IPCs and four CPCs relevant to the search topic stood out (Table 1). However, in the logical expression, according to the ORBIT[14] syntax system, such classifications were used up to the "subclass" level, in order to define the scope of prospecting (Table 2).

Subsequently, specific keywords were selected to build a list of strings, according to the ORBIT Intelligence syntax system, with the aim of optimizing the patent prospecting process for technological solutions dedicated to COVID-19 associated with CRISPR-Cas, ACE2 and Spike (Tables 1 and 2).

Table 1. IPC and CPC identification strategy related to COVID-19

IPC/CPC/ Search Parameter	**Result**
IPC/COVID-19	A61L 2/22: Phase substances, i.e., smokes, aerossols [2006.01] A61L 9/14: Usage of vaporized or pulverized substances [2006.01] A61K 39/215: Coronoviridae, i. e., avian infectious bronchitis virus [2006.01] A61K 38/16: Peptides longer than 20 aminoacids; Gastrins; Somatostatins; Melanotropins; their derivatives [2006.01] A61K 39/12: Viral antigens [2006.01]
IPC/COVID-19	A61K 39/00: Medicinal preparations containing antigens or antibodies (materials for immunotrials G01N 33/53) [2006.01] A61K 48/00: Medicinal preparations containing genetic material inserted in cells from live beings to treat genetic diseases; Genetherapy [2006.01] A61K 38/00: Medicinal preparations containing peptides (peptides containing betalactame rings A61K 31/00; cyclic dipeptides lacking any other peptide bonds besides the ones found in the ring formation, i.e., piperazine-2.5-diones, A61K 31/00; ergoline-based peptides A61K 31/48; that contains macromolecular compounds with aminoacid units statistically distributed A61K 31/74; medicinal preparations containing antigens or antibodies A61K 39/00; medicinal preparations characterized by the non-active ingredients, i.e., peptides as drug carriers A61K 47/00) [2006.01] A61K 39/12: Viral antigens [2006.01] A61K 39/395: Antibodies (aglutinins A61K 38/36); Immunoglobulins; Immunoserum, p. ex. Anti-lymphocitic serum [2006.01]
CPC/COVID-19	A61K2300/00Mixtures or combinations of active ingredients, wherein at least one active ingredient is fully defined in groups A61K31/00 - A61K41/00

Source: own elaboration, based on the study of data retrieved from the IPC and CPC databases (IPC data - http://ipc.inpi.gov.br/ and https://www.wipo.int/classifications/ipc/ipcpub; CPC data - https://worldwide.espacenet.com/classification?locale=en_EP)

2.2 PATENT PROSPECTION

The prospecting of patent databases was carried out in the ORBIT Intelligence system, owned by the Franco-American company Questel and in the COVID-19 Observatory of the National Institute of Industrial Property[15] (INPI). The document databases chosen for mining were all from the ORBIT system, which represent more than 96 countries. The search strategy, according to the ORBIT Intelligence System, was carried out through a logical expression construction or search query to obtain a wide range of patented technologies (Supplementary Material[2]. For patent prospection, five strategies were used. However, the first was not considered for the final quantification of patent families because the results obtaining with this strategy was incorporated in the results originated by the second strategy. Thus, 112 patent families were identified "related" to COVID-19 associated to CRISPR-Cas, ACE2 and Spike. Consider "related" to "some degree of pertinence" (Table 2).

Table 2. Prospection Strategies for CRISPR-Cas, ACE2 e Spike associated to COVID-19 and number of recovered patent families

Prospection subject	**Number of recovered patent families**	**Prospection source**
Identify technologies on COVID-19	07	ORBIT (2021)[14]
Identify technologies on COVID-19 associated to CRISPR-Cas, ACE2 e Spike	23	ORBIT (2021)[14]
INPI COVID-19 Observatory	10	Weid (2021)[16]
INPI COVID-19 Observatory	02	Mendes (et al. 2020)[17]
INPI COVID-19 Observatory	12	OEPM (2020)[18]
INPI COVID-19 Observatory	05	INPI (2021)[14]
INPI COVID-19 Observatory	05	Mendes (et al. 2021)[19]
INPI COVID-19 Observatory	09	Silva (2021)[20]
INPI COVID-19 Observatory	08	Ferraz (2021a)[21]
INPI COVID-19 Observatory	04	Weid (2021)[22]
INPI COVID-19 Observatory	02	Ferraz (2021b)[23]
Identify technologies on COVID-19 associated to CRISPR-Cas, ACE2 e Spike	25	WIPO (2022)[24]
TOTAL	**112**	-

Source: own elaboration.

The patent families recovered do not refer specifically to COVID-19, they were recovered recently and were all deposited (application) on dates before the beginning of the pandemic and therefore were developed for different applications. In some cases, it could even be applied for COVID-19, as a secondary use. The technical problems (or applications) that the patent families obtained from the ORBIT system database aim to target/solve: Parkinson's disease, cancer, cornea dystrophy, aberrant angiogenesis, antibiotics, antiviral, cellular

[2] https://bit.ly/3C9WKej

regeneration, induced pluripotent stem cell, bactericide irradiation, modified RNA, personalized hepatocyte. On the other hand, the applications identified in the patent family recovered in the INPI COVID-19 Observatory are: SARS-CoV-1, bovine coronavirus, feline infectious peritonitis (feline coronavirus), canine infectious disease, that will be presented in the next session, are indeed about COVID-19, therefore, absolutely up-to-date.

In this sense, in the future, a new patent-driven mining process on COVID-19 to privilege the comparative analysis between the clinicals tests and patent development. In this manner, it will be possible to compare registered technological solutions in the patent family for the COVID-19 technical problem and, finally, based on the patent application, verify which clinical trials were developed for a similar target.

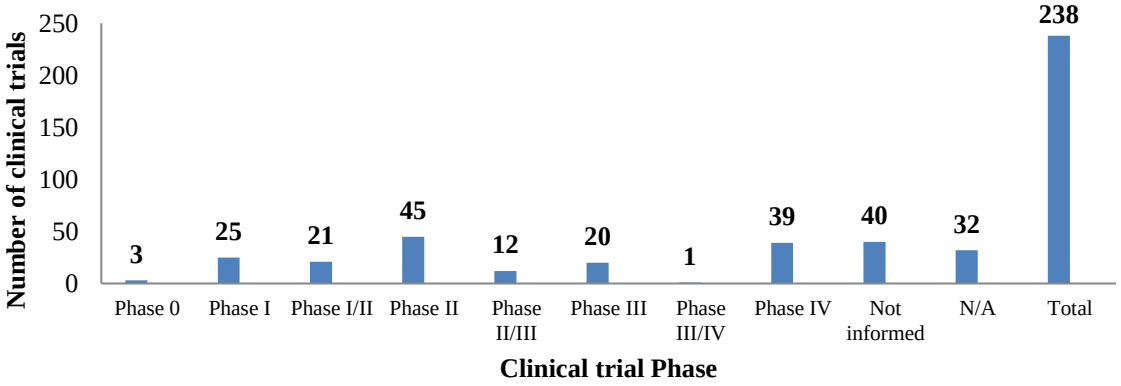
2.3 CLINICAL TRIAL PROSPECTION

The prospecting of clinical trials databases was carried out by simulation on the WHO International Clinical Trials Registry Platform[25], which represents more than 120 countries. Searching was carried out following a step-by step provided by the platform. It is noted that data on 61 clinical trials on COVID-19 were recovered worldwide on an 8 months' time frame.

3 RESULTS

It is noteworthy to register that, according to the search configuration, 61 clinical trials were recovered. In the sequence, ten indicators were elaborated from the *ICTRP* mined data. The profile retrieved from the ICTRP on the total number of COVID-19 clinical trials associated with CRISPR-Cas, ACE2 and Spike for each phase of each identified category can be seen in Figure 1. In a universe of 238 clinical trials, some points deserve emphasis. The highest number contributors are from clinical trials identified as "Phase I/II", a tie between "Phase I, II and N/A (not applicable)"; and the "Phase I/II" category. Another relevant aspect resides on the fact that 23% of the clinical trials are in transition between phases "I to II" and "II to III", which in turn demonstrate a positive dynamic profile of the clinical trials, and 26.2% from the clinical trials were not identified precisely because they are classifies in a status of categoric cloudiness, represented by "N/A" and "not informed". But we can affirm that 13% of the clinical trials are in a more advanced stage or with a more conclusive profile because they were not represented by Phases III and IV.

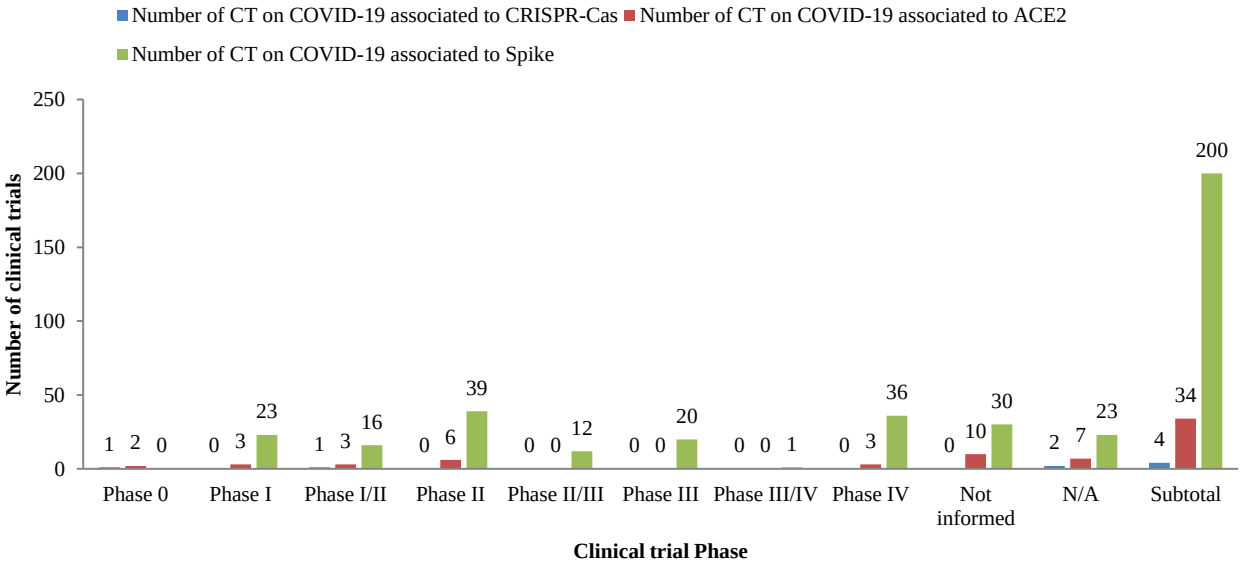
Figure 1. Number of clinical trials (CT) by phase on COVID-19 associated to CRISPR-Cas, ACE2 and Spike.



Source: own elaboration based on the data retrieved from the ICTRP platform[25].

The number and respective percentage of clinical trials on COVID-19 categorized into 3 types of technology: CRISPR-Cas, ACE2 and Spike can be seen in Figure 2. The highest numbers were for the clinical trials categorized as Phase I, II and II/III; and ACE2 in Phases "N/A" and "Not informed", that together represent 52.5% from all clinical trials. Another important aspect resides in the fact that the Spike technology is in transition phase "I to II" and "II to III", and they sum up 18% of the clinical trials, and the CRISPS-Cas technology is found solely in Phase 0 and represents only 1.6% of all clinical trials.

Figure 2. Number of clinical trials (CT) on COVID-19 categorized by technologies: CRISPR-Cas, ACE2 and Spike by clinical trial phase.



Source: own elaboration based on the data retrieved from the ICTRP platform[25].

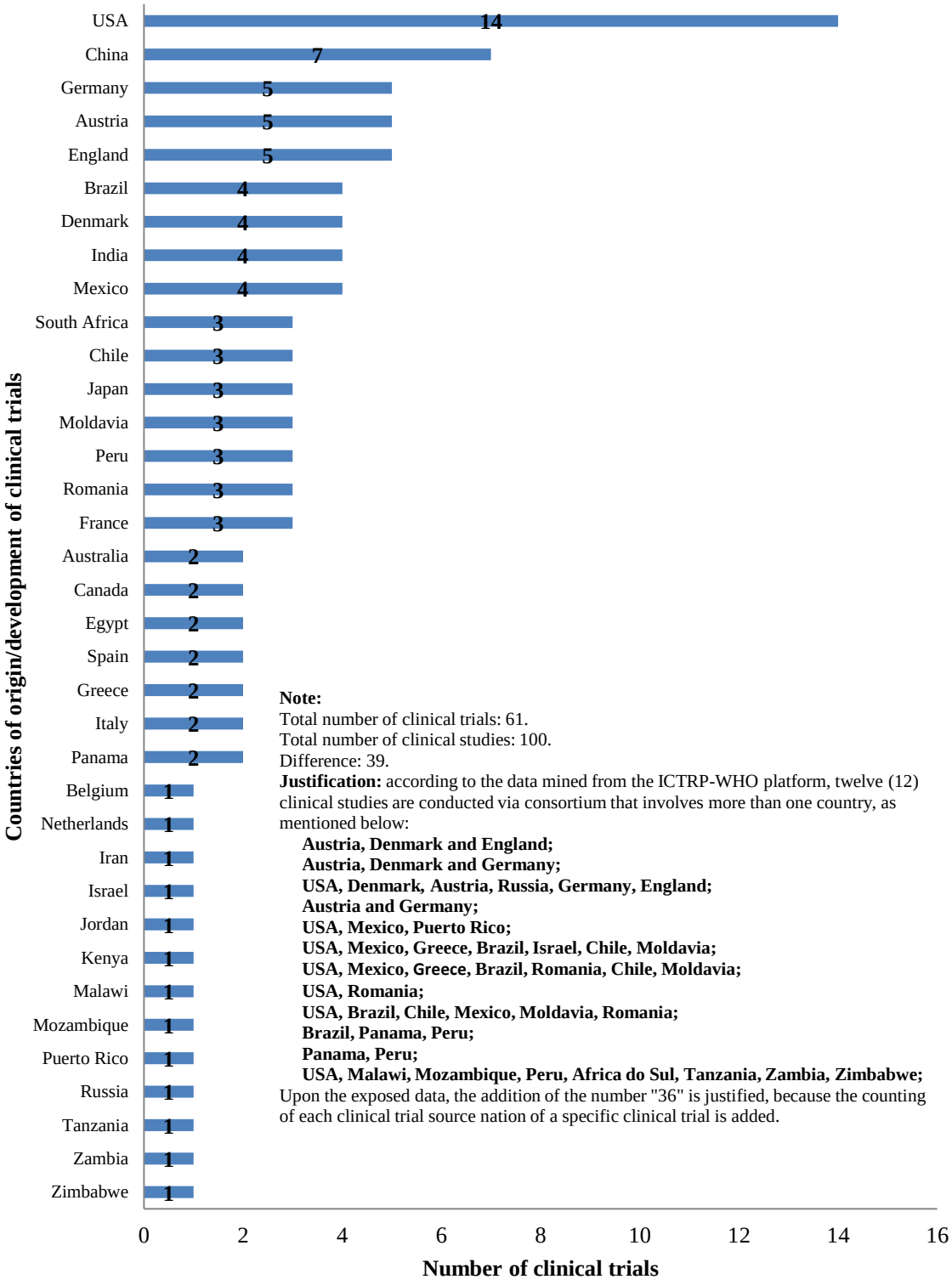
In relation to main sponsors, there are 41 institutions that act as main sponsors, among which *Novavax* (USA) and *Regeneron Pharmaceuticals* (USA) dominate the field, each with

8.2% of all clinical trials (Supplementary Material 3A[3]. In relation to main sponsors, there are twelve that drive clinical trials, from which two corresponds to 5% and 3.3%, respectively, and the remainder are responsible for 1.6% on the total worldwide clinical trials numbers. The types of secondary sponsors are distributed equally for each of them, with 16.7% being philanthropic institutions, research centers, private companies, hospital associated to university; with 25% universities and 8.3% hospitals, Supplementary Material 3B[4].

Figure 3 shows the clinical trial in relation to their country of development, in absolute numbers related to their contribution. It is shown a total of thirty six countries, distributed in five continents. There are nine main nations, in the following order, the USA with 23% of all clinical trials, China with 11.5%, Germany, Austria and England with 8.2% each and ranked in fourth are Brazil, Denmark, India and Mexico, each with 6.6% of the total clinical trials. It is important to clarify that these nine dominant countries account for 85.5% of main 61 clinical trials on COVID-19 associated to CRISPR-Cas, ACE2 and Spike, conducted in the world in the las fourteen months. Another aspect that deserves to be highlighted is the fact that 66.7% of the countries participate in clinical trials through consortiums and this organization responds for 93.8% of the clinical trials.

[3] https://bit.ly/3C728if
[4] https://bit.ly/3C728if

Figure 3. Number of clinical trial (CT) on COVID-19 via CRISPR-Cas, ACE2 and Spike according to their country of origin/development

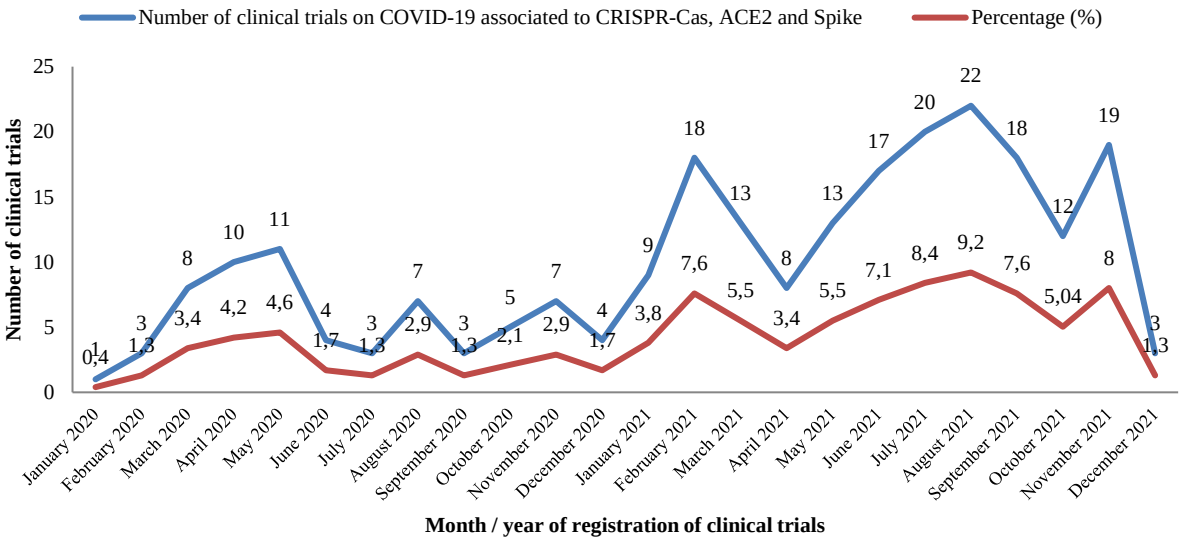


Source: own elaboration based on the data retrieved from the ICTRP platform[25].

In Figure 4 we show the month of the clinical trial registration on COVID-19 via CRISPR-Cas, ACE2 and Spike in the years of 2020 and 2021, in absolute numbers and percentage. It is also shown a linear growth with the maximum peak value in May 2020, with

18% of all clinical trials. The minimum peak was in January 2020 with 1.6% of all clinical trials, followed by the months of June, July and September, each of which accounts for 5%. Mister highlights that, despite the fact that the pandemic challenge is recent, one can identify four inflexion points that portraits increasing interest in the clinical development to treat COVID-19 via CRISPR-Cas, ACE2 and Spike, what most likely is justified by the expressive worldwide impact in health, politics and economy, what induces the interest/pharmaceutical company funding (traditionally hegemonic) in adopting a permanent agenda on combat to COVID-19.

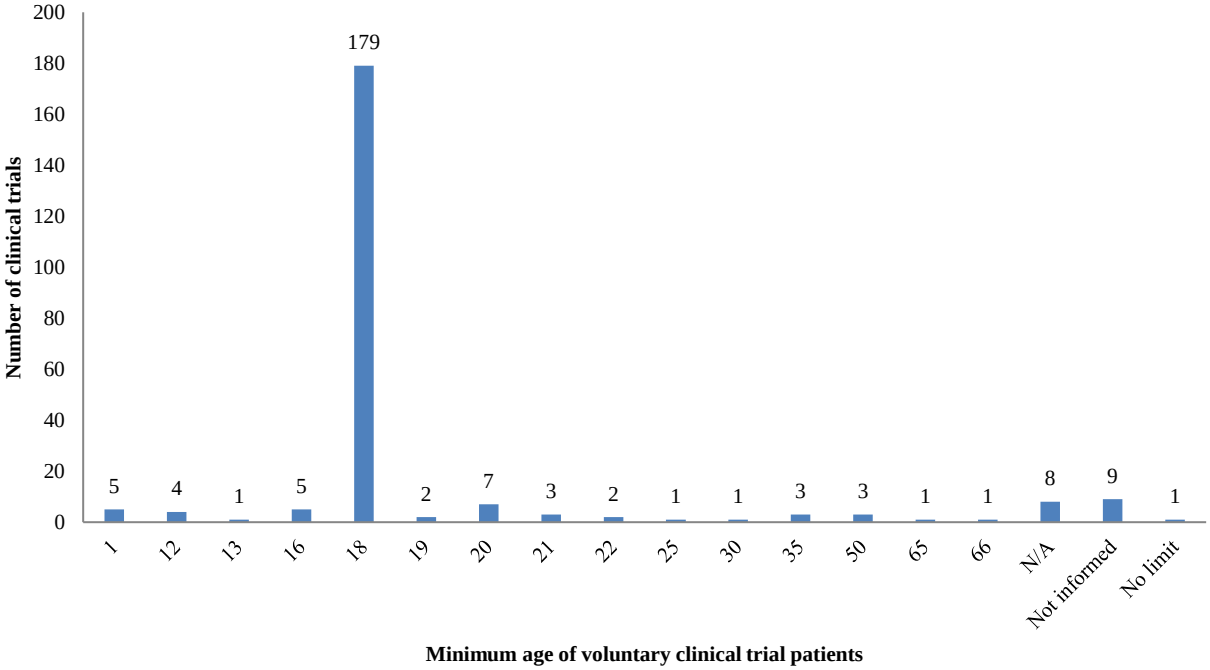
Figure 4. Number of clinical trials (CT) on COVID-19 via CRISPR-Cas, ACE2 Spike per month



Source: own elaboration based on the data retrieved from the ICTRP platform[25].

Clinical trials of COVID-19 via CRISPR-Cas, ACE2 and Spike according to the minimum age of volunteer patients can be seen in Figure 5. Eleven (11) types of minimum age were identified, the age being “18 years old” the most expressive profile that meets 75.4% of all clinical trials.

Figure 5. Number of clinical trials (CT) on COVID-19 via CRISPR-Cas, ACE2 and Spike per minimum age

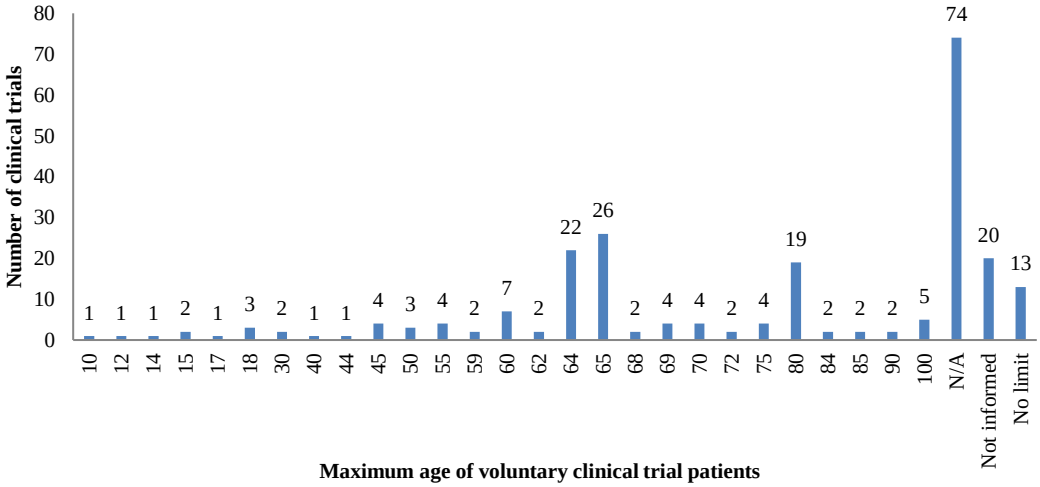


Source: own elaboration based on the data retrieved from the ICTRP platform[25].

Figure 6 quantifies in absolute numbers of clinical trials on COVID-19 via CRISPR-Cas, ACE2 and Spike according to maximum age of voluntary patients. Seventeen types of maximum ages were identified in the ages of: “65 years”, “80 years”, “N/A” and “Not informed” and together they represent 72.1% of all clinical trials. When comparing Figures 5 and 6, it is detectable that 35.3% more maximum age profiles were stablished.

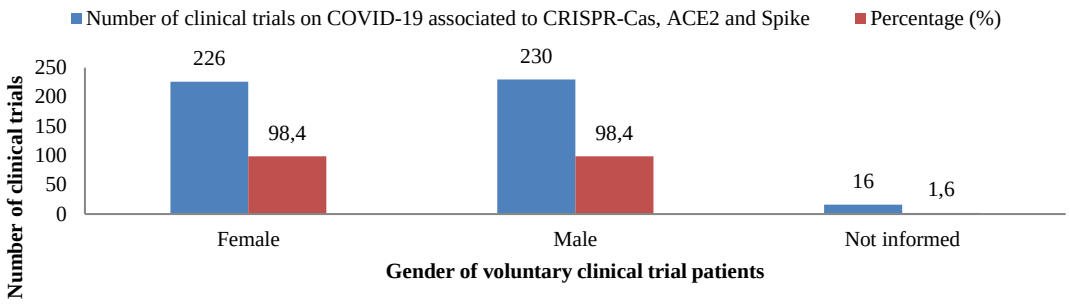
Data associated with the gender of volunteer patients can be seen in Figure 7. Three profiles were identified, two of which were quantitatively identical.

Figure 6. Number of clinical trials (CT) on COVID-19 via CRISPR-Cas, ACE2 and Spike per maximum age



Source: own elaboration based on the data retrieved from the ICTRP platform[25].

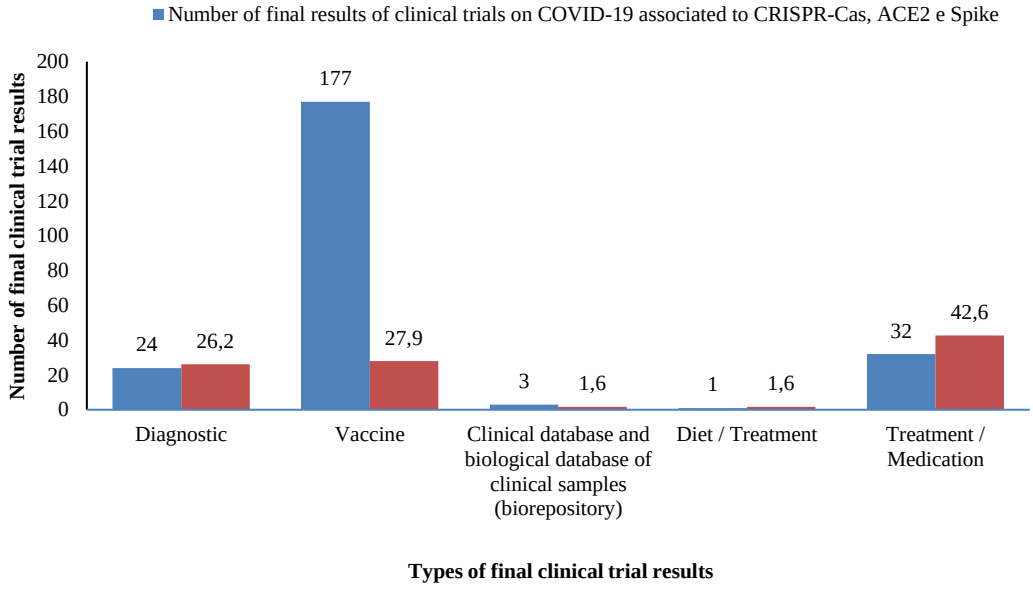
Figure 7. Number of clinical trials (CT) on COVID-19 via CRISPR-Cas, ACE2 and Spike per gender



Source: own elaboration based on the data retrieved from the ICTRP platform[25].

In Figure 8, we show five types of final clinical trial results on COVID-19 via CRISPR-Cas, ACE2 and Spike. It can be observed an expressive representation of three technological categories: "treatment/medication" and a technical tie between "diagnostic" and "vaccine", that represent 42.6%, 26.2% and 27.9%, respectively, based on the quantification of the clinical trials, and, thus, portrait all the clinical-technological to fight COVID-19 via CRISPR-Cas, ACE2 and Spike.

Figure 8. Number of clinical trials (CT) on COVID-19 via CRISPR-Cas, ACE2 and Spike per final result.



Source: own elaboration based on the data retrieved from the ICTRP platform[25].

The profile of the data retrieved from the technological prospection carried out in the ORBIT system and in the ICTRP platform can be observed in Supplementary Material 4[5]. Of

[5] https://bit.ly/3Govf3l

the forty-five assignees of patent families, it is worth mentioning that only Regeneron Pharmaceuticals is present among the forty-five a major sponsor of clinical trials.

Through other words there is an unexpressive portfolio of institutions with this double profile (sponsor and owner) on technologies to fight COVID-19 via CRISPR-Cas, ACE2 and Spike, even knowing that the patent families do not exactly refer to technological solutions directed to the technical problem recently named COVID-19. In a certain way there is a mismatch between the institutions that invest funds to fight the coronavirus family, be it in the patent perspective, be it in the clinical trial perspective.

The high matrix sparsity (element nullity), together with the "unitary" tax of concatenation between both portfolios presuppose uninterest (or low technological maturity) from the "pharmaceutical industry" in the development and practical implementation of new technologies anti-COVID-19 (or even anti-COVID-family) via CRISPR-Cas, ACE2 and Spike. Despite both portfolios present a shy interaction, almost all institutions are based in hegemonic nations, which suggests the "market reserve" practice, through which the production and commercialization of technology by a third party is limited or halted.

In summary, such knowledge supports the known practice of the pharmaceutical industry and the big research centers, that invest expressively in a solid and robust patent portfolio, with the aim to grant commercial exploration exclusivity in the drug market and other technologies applied to health (diagnostic and vaccine).

In Table 3 is shown the evolution of clinical trials through a fourteen-months period and of patent families through two decades. The justification and relevance of the choice of parameters were of a different nature, such as the years of registration of clinical trial, first unionist priority, first deposit (application) and first publication, the last three of patents families. It's worth clarifying that the unionist priority year (first deposited patent request according to the 4th article from the Paris Union Convention, the 1883 PUC[26] (França 1883), a concept incorporated in the Brazilian judicial ordering through article 16 located in the Law Nº 9279[27], from May 14th, 1996, that "regulates the rights and obligations relative to industrial property"), lies on the strategic fact that demonstrates the starting year of intention or interest in the technological development, via patent families, in solving certain technical problems.

Once again, the disproportionality is confirmed between the clinical trials and patents portfolios, but the sparsity degree on clinical trials must not be considered since COVID-19 actually appeared on October 2019.

The temporal sparsity of the patent families is 50%, 54.5% and 45.5% in the temporal axis when it relates to unionist priority, first deposit (application) and first publication,

respectively. It is understood that, *a priori*, in light of the worldwide burden under study, it becomes infectible due to the contrast between both portfolios due to the reason aforementioned, because the recovered patent families in the screen study refers to technical problems solutions previous to COVID-19.

But, in summary, it is deduced that the behavior pattern of "dates types" of recovered patents present "discontinuities" and inflexion points with unexpressive oscillation, however with constant and insipid general profile. In summary, with the exception of the data from the previous two years (2019-2020) of both portfolios, that are in consolidation due to legal and administrative deadlines (confidentiality period), it is possible to notice a tendency of fragile interest on the clinical trials and a lack of interest for the patents on "coronavirus" via CRISPR-Cas, ACE2 and Spike, even prior to COVID-19.

Table 3. Time frame com parison between clinical trials (CT), priority, deposit/application and publication of patent families (PF)

Year	Nº of CT	Nº patent family (PF) / year		
		1st unionist priority	1st application	1st publication
1999	00	00	00	00
2000	00	00	00	01
2001	00	01	00	00
2002	00	00	03	00
2003	00	07	00	00
2004	00	01	05	04
2005	00	03	00	00
2006	00	00	03	04
2007	00	02	00	02
2008	00	00	02	02
2009	00	01	01	01
2010	00	01	00	00
2011	00	00	01	01
2012	00	00	00	00
2013	00	00	00	00
2014	00	03	00	00
2015	00	07	03	01
2016	00	07	05	01
2017	00	07	06	05
2018	00	02	01	06
2019	00	00	02	05
2020	60	01	01	01
2021	01	00	00	00

Source: own elaboration with data from [14, 17, 18, 22, 25].

With regard to national and regional patent offices, a total of 40 were identified, 38 of which were national and two regional. Clinical trial portfolios across geographic dispersion are concentrated in the top 10% of nations, Supplementary Material 5[6].

As previously mentioned, although sixty-one recovered clinical trials are targeted to COVID-19 associated to CRISPR-Cas, ACE2 and Spike, forty one patent families recovered are not specifically targeted to COVID-19 since they had priority dated before the pandemics. In other words, such patent families were developed to solve different technical problems, such as Parkinson's disease, cancer, cornea dystrophy, aberrant angiogenesis, antibiotics, cellular regeneration, induced pluripotent stem cell, bactericide irradiation, modified RNA, personalized hepatocyte, SARS-CoV-1, bovine coronavirus, feline infectious peritonitis (feline coronavirus), canine infectious disease, Alzheimer's disease, antiviral.

Furthermore, current clinical trials (61 up to 01/20/2021), will probably be part of patent families in the next 10 years, considering the dynamics of the development of pharmacological technologies (medication) and non-pharmacological (vaccines and diagnostic devices) necessary for clinical trials, regulatory sanitary authorizations and patent deposits/applications.

In this sense, in the future, a new patent mining will be performed specifically for COVID-19 to privilege the comparative analysis between clinical trials and patent development. In this manner, it will be possible to compare the technological solutions registered in the patent families specific for the COVID-19 technical problem. It will then be possible to verify, based on the patent application, which clinical trials performed targeted to similar goal (technical problem solution intended to be solved by the clinical trial and the patent request).

4 CONCLUSIONS

In light of the analysed results, we conclude that the global scenery on clinical trials and patent families, both applied to COVID-19 via CRISPR-Cas, ACE2 and Spike, points toward a path that imposes the urgent need to build new public policies that can support such demands. In the case of Brazil, it is important to note the need of a follow up on the Senate's Law Project Nº 200 [28], that "dictates principles, guidelines and rules for clinical research in humans performed in public or private institutions", and the INPI Resolution Nº 239 [29].

It's also important to register all the efforts around the Law Nº 9279 [27], that "regulates rights and obligations relative to industrial property", in a sense to improve the patent system

[6] https://bit.ly/3YWADBO

in the country, through funding that stimulate the increase in the patent portfolio of "Brazilian priority", in form of the INPI Resolution Nº 237 [30], increase the number of conceded national patents, reduce the average time in patent concession in Brazil, according to the INPI Resolution Nº 240 [31] and with INPI Resolution Nº 241 (*backlog*) [32]. In summary, it is understood that the synergetic combination of the effects (social, economic, and judicial) of these two legal diplomas can significantly impact on the technological independence of Brazil in the sense of the creation of new technologies to fight COVID-19 via CRISPR-Cas, ACE2 e Spike.

The broad scenery on the fight against COVID-19 via CRISPR-Cas, ACE2 and Spike have 238 clinical trials and 112 patent family, that are not related to COVID-19, but can indicate a second use possibility because they are targeted to solve some technical problems that possess some degree of similarity when it comes to fight other known viruses from the coronavirus family.

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