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Clinical trials of COVID-19 vaccine development: a global overview

Ensaios clínicos de desenvolvimento de vacinas contra a COVID-19: uma visão global

Ensayos clínicos de desarrollo de vacunas contra el COVID-19: una descripción general

João Victor Antunes Lopes [1]
André Luiz Sica de Campos [2]
Rafael Rodrigues de Moraes [1]
Luciana Correia Alves [1]

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Abstract

This study aims to report analyses regarding the global distribution of institutions involved in clinical trials of COVID-19 vaccines throughout February 2022. We retrieved global data from the World Health Organization report on vaccine development. These data allowed us to identify project institutions and plot their geographic coordinates. We produced a georeferenced map using an R programming environment and, based on the geographical location of vaccine developers, we analyzed the subcontinental distribution of clinical trials and the nature of the vaccines. Regionally, South-Southeast Asian countries carried out more clinical trials than any other region, proportionally, although this happened solely for mature technologies. Few trials were under implementation in Latin America and Africa. Our findings confirm previous studies on the regional concentration in the development of technology. However, our contribution lies in showing these phenomena for COVID-19 vaccines in specific subcontinents and technologies, at a country level. Our data underscores which subcontinents perform very few clinical trials for COVID-19 and seem to be ill-prepared for future disease outbreaks, and if these become epidemics or even pandemics and require domestic vaccine development or production. We also consider the case of Brazil, which did not finish the complete cycle of COVID-19 vaccine development in the indicated period; but, with favorable policies, it has potential to engage further in COVID-19 vaccine technology.

COVID-19; Vaccines; Vaccine Development

Correspondence
J. V. A. Lopes
Instituto de Filosofia e Ciências Humanas, Universidade Estadual de Campinas.
Rua Cora Coralina 100, Campinas, SP 13083-896, Brasil.
joao-victor.antunes@hotmail.com

[1] Instituto de Filosofia e Ciências Humanas, Universidade Estadual de Campinas, Campinas, Brasil.
[2] Faculdade de Ciências Aplicadas, Universidade Estadual de Campinas, Campinas, Brasil.

Introduction

Efforts for the development of a vaccine for COVID-19 gained momentum when the World Health Organization (WHO) declared a global pandemic on March 11th, 2020 [1]. An intensified global mobilization for the development of such vaccine ensued. On December 22nd, 2020, in record time, vaccines such as Sputnik V (Russia), Pfizer/BioNTech (United States/Germany), and Sinovac-CoronaVac (China) were in use; 61 vaccines were in clinicals trial and 172 in pre-clinical trials – these figures increased to 140 and 194, respectively, by February 2022 [2].

Public agencies, public research institutes, universities, and private organizations established partnerships to develop vaccines. Alliances and cooperation among these agents allowed for the articulation of complementary technical capacities, e.g., in the field of Biotechnology [3,4,5].

Evidence showed that vaccine development took place in record time, but also in an unequal manner among different countries and occurred predominantly in developed countries [6]. Likewise, the global distribution of immunizers leaves regions and countries behind, in such a way that only 0.2% of the vaccine doses administered by April 2021 were delivered to inhabitants of low-income countries [7]. By March 2022, only 1% of the vaccine doses administered had reached those countries [8]. Furthermore, the risk-averse pharmaceutical companies relied on ill-coordinated public funding, facing a challenging supply chain [9].

The effective control of the pandemic requires improved regional alignment and involvement of the Global South in vaccine research and development, especially considering pandemic epicenters in countries whose capacity for vaccine development is relatively limited (e.g., South America) [6]. In this context, our study maps the distribution of the institutions involved in clinical trials for COVID-19 vaccine globally. Based on the geographical location of vaccine developers, we aimed to analyze the global distribution of vaccine development projects in clinical trials. We then identify patterns of international distribution of the vaccine developers involved in clinical trials according to data recorded by the WHO.

We base our analysis on the point of view that vaccine development is a broad process, in wich many complex and complementary stages are required to accomplish novel pharmaceutical innovation [10]. Vaccine development starts with scientific discovery, wich evolves, and interacts with preclinical development and in vitro tests of active ingredients. Here, we focus on a key innovation stage: the clinical trials phase.

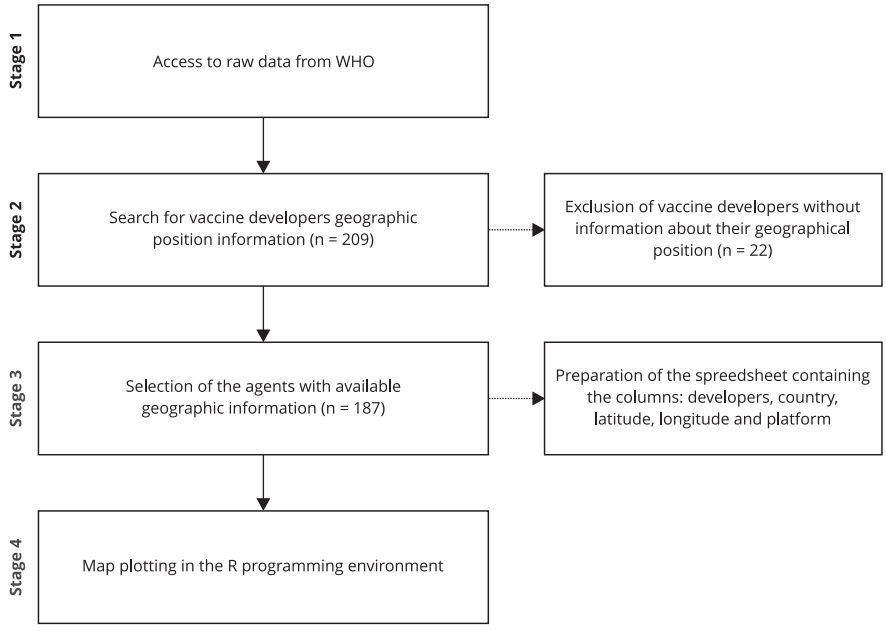
Methods

All institutions listed as vaccines developers by the WHO and involved in the clinical trials of COVID-19 vaccine development were tabulated based on data from the WHO report COVID – Landscape of novel coronavirus candidate vaccine development worldwide [2] (updated on February 1st, 2022).

Figure 1 shows the methodological stages employed in this study. In total, 140 vaccine projects in the clinical trials for COVID-19 were identified worldwide based on data issued by the WHO from the onset of the pandemic up to February of 2022 (Stage 1). These projects involved 209 vaccine developers. Data were collected on their geographic coordinates (latitude and longitude) (Stage 2). Of the 209 vaccine developers, 22 were excluded due to the non-availability of latitude and longitude data (Stage 3). Thus, the sample consisted of 187 developers, for which a spreadsheet was created, whose columns are shown in Figure 1, Stage 3. A georeferenced map was created (Stage 4) in the R programming environment, version 4.2.1 (http://www.r-project.org).

Figure 1

Flowchart of the methodological stages.



WHO: World Health Organization.

Results

Table 1 shows that the United States and China accounted for 27.27% and 20.32% of the vaccine developers participating in the clinical trials, respectively, followed by England (5.88%), Japan (4.28%), and Canada (3.74%). Austria, Brazil, Indonesia, Norway, Vietnam and The Netherlands occupy the next-to-last position (1.07% each), whereas Saudi Arabia, Belgium, Kazakhstan, Singapore, Egypt, Spain, Israel, Mexico, Myanmar, Taiwan, and the Republic of Uganda are in last place (0.53% each).

The distribution of vaccine development by country shown in Table 1 reveals the regional involvement in these activities. We performed a subcontinental analysis and assumed clinical trials to be related to the different stages of technological development of vaccines, as mentioned above. The evidence points to a concentration of vaccine developers participating in clinical trials at the subcontinental level and, within subcontinents, we identified a fragmentation at the national level. North America (United States and Canada) (31.01% of clinical trials) follows closely, in the number of institutions, to South-Southeast Asia (combining China, Japan, India, South Korea, Thailand, Myanmar, Vietnam, Taiwan, and Singapore) (34.76%) (Table 1). Western Europe appears behind those regions (England, Germany, France, Italy, Austria, Norway, Spain, The Netherlands, and Belgium) (16.58%) (Table 1). On the latter two subcontinents, vaccine developers are dispersed among several countries. Other vaccine developers reported by the WHO (17.11%) were in what we call "rest of the world", such as the Middle East (Iran, Turkey, and Saudi Arabia) (5.88%), Latin America (Cuba, Brazil, and Mexico) (3.74%), Central Asia (Russia and Kazakhstan) (3.21%), Oceania (Indonesia and Australia) (3.21%), and Africa (Egypt and Uganda) (1.07%) (Table 1).

Table 1

Absolute and relative distribution (%) of clinical trials from vaccine developers for COVID-19 by country.

Country	Absolute frequency	%
United States	51	27.27
China	38	20.32
England	11	5.88
Japan	8	4.28
Canada	7	3.74
India	6	3.21
Iran	6	3.21
Germany	5	2.67
South Korea	5	2.67
Russia	5	2.67
Australia	4	2.14
Cuba	4	2.14
France	4	2.14
Turkey	4	2.14
Italy	3	1.60
Thailand	3	1.60
Austria	2	1.07
Brazil	2	1.07
Indonesia	2	1.07
Norway	2	1.07
Vietnam	2	1.07
The Netherlands	2	1.07
Saudi Arabia	1	0.53
Belgium	1	0.53
Kazakhstan	1	0.53
Singapore	1	0.53
Egypt	1	0.53
Spain	1	0.53
Israel	1	0.53
Mexico	1	0.53
Myanmar	1	0.53
Taiwan	1	0.53
Republic of Uganda	1	0.53
Total	187	100.00

Source: prepared by the authors, based on data from World Health Organization [2].

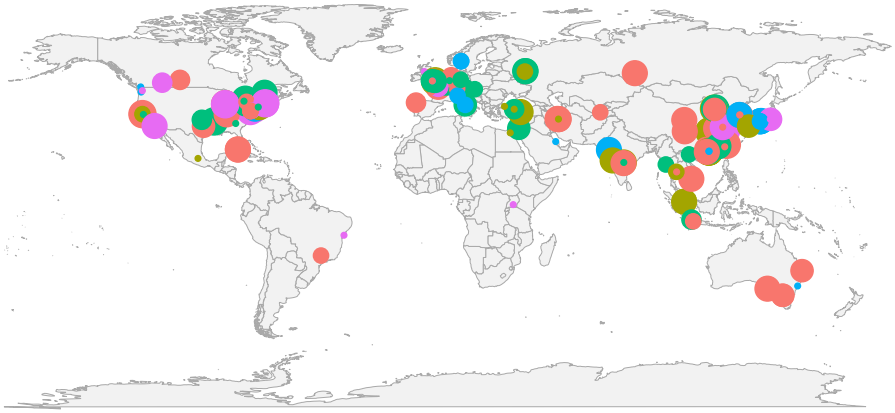
Discussion

Our findings are consistent with studies on the globalized development of technology, which indicates a trend toward the development of technologies in specific regions [11,12,13]. This suggested a concentration in North America, Western Europe, and Japan followed by a fragmented regionalization of the development of technology [12,13], which seems to be reflected in our data.

We identified a concentration of vaccine developers in North America, Western Europe, and South-Southeast Asia. Hence, technological activities are regionally concentrated but fragmented in different countries within these regions. In qualitative terms, Figure 2 shows the maturity of the vaccines tested. North America and Western Europe concentrate clinical trials on more modern vaccine technologies (e.g., messenger RNA and the recombinant viral vector), South-Southeast Asia seems to focus on more mature technologies (e.g., attenuated/inactivated virus or protein subunits).

Figure 2

Global distribution map of clinical phase and platform of vaccine development for COVID-19.



Source: prepared by the authors, based on data from World Health Organization [2].

Ghattas et al. [14] considers MRNA and DNA vaccines novel platforms based on biotechnological techniques that are faster to develop and generate a more robust immune response than vaccines based on inactivated and attenuated pathogens. The latter two have been available for a longer period, take longer to be developed into specific vaccines, and have more limited immune responses. Taken together, these elements indicate the international distribution of clinical trials as a proxy for involvement in vaccine development in modern or mature technologies, by different institutions, countries, and regions.

We note the secondary role of Brazil compared to Russia, India, China, and Cuba. Besides, Latin America and Africa present extremely low figures regarding clinical trials. Our data suggest the absence of clinical trials in Eastern Europe. This underscores the need for such activities in these regions in order to respond to future pandemics. International efforts in vaccine development could be better aligned, so that regions lagging begin to take part in clinical trials. Brazil's secondary position and its efforts to respond to COVID-19 [15] suggest it as a case that has not finished the full cycle of the COVID-19 vaccine development, but given favorable policies, has the technological maturity (within Oswaldo Cruz Foundation – Fiocruz, and Butantan Institute) to engage further in technologies for COVID-19 vaccines. It should be noted that the characteristics of the production plants of the Butantan Institute and Fiocruz put Brazil's health industrial complex in a prominent place to accomplish this [16].

Final considerations

This study provides an overview of the global distribution of the development of vaccines in the clinical trial phase for COVID-19. The results are coherent with observations made by Thanh Le et al. [6] regarding the concentration of the development of immunizing agents for COVID-19, mostly in developed countries and China.

Our contribution consisted in the identification of the subcontinents and countries in leading positions regarding the different technologies tested and describing the pattern of this phenomenon. The findings show that the COVID-19 vaccine development projects in the clinical trial phase are concentrated in South-Southeast Asia (mature technologies), followed by North America (modern technologies), and Western Europe (modern technologies). An accentuated fragmentation is found at the national level in the latter two regions. These results confirm the findings of previous studies on the relative concentration of the international distribution of technological development. This trend shows a global scenario of considerable inequality in terms of improvements in public health for subcontinents with relatively limited capacity to respond to future pandemics. Clinical trials should be intensified, integrating regions excluded from testing activities – this calls for increased regional alignment in vaccine development.

We recognize the development of active pharmaceutical ingredients and manufacturing process adaptation and learning as equally relevant and complex when compared to clinical trials. We also acknowledge that an intricate supply chain was articulated globally and in record time, with drug substance being a key input manufactured by a few producers in an oligopolistic fashion [17,18]. However, to cover these issues would be beyond our goal, and our interest lied solely on clinical trials, spreading over different clinical test phases [19]. Clinical trials involve a combination of financial and technical resources, regulatory and scientific expertise, as well as the availability of active cases for study and remain a key bottleneck in vaccine development with the potential to benefit participating institutions, countries, and regions. Much potential exists for participating countries in benefiting from clinical trials in terms of integrating international scientific networks and more readily access to novel vaccine technologies, as previewed in the *Helsinki Declaration*. Participation in such studies show, to international partners, the existence of local expertise in this domain [20].

Weak participation in clinical trials is noted in both Latin America and Africa, with a virtual absence of projects in Eastern Europe. One should reflect on the impact of COVID-19 in these regions, considering the dependence on the supply of immunizing agents by private companies and foreign governments. In opposition to such dependence, engaging actively in vaccine development and production could be a better way to face the effects of future disease outbreaks, epidemics, and even pandemics.

Contributors

J. V. A. Lopes contributed to the study conception, data collection, organization and analysis, interpretation and discussion of the results, writing and review, and approved the final version of the manuscript. A. L. S. Campos contributed to the study conception, data analysis, interpretation and discussion of the results, writing and review, and approved the final version of the manuscript. R. R. Moraes contributed to the organization and analysis of data and approved the final version of the manuscript. L. C. Alves contributed to the analysis and discussion of the results, wrote and provided a critical review, and approved the final version of the manuscript.

Additional information

ORCID: João Victor Antunes Lopes (0000-0002-1283-7321); André Luiz Sica de Campos (0000-0002-6801-0454); Rafael Rodrigues de Moraes (0000-0002-5782-3839); Luciana Correia Alves (0000-0002-8598-4875).

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Resumo

O objetivo desta comunicação é relatar análises sobre a distribuição global das instituições envolvidas em ensaios clínicos relacionados às vacinas de COVID-19 até fevereiro de 2022. Obtivemos dados globais da Organização Mundial da Saúde sobre o desenvolvimento de vacinas. Isso nos permitiu identificar as instituições de projetos e traçar as suas coordenadas geográficas. Produzimos um mapa georreferenciado usando a linguagem de programação R e, a partir da localização geográfica dos desenvolvedores de vacinas, analisamos a distribuição subcontinental dos ensaios clínicos e a natureza das vacinas testadas. Regionalmente, os países do Sul-Sudeste Asiático realizaram proporcionalmente mais ensaios clínicos do que qualquer outra região, embora isso tenha acontecido para tecnologias maduras. Poucos ensaios estavam em fase de implementação na América Latina e na África. Nossos achados confirmam estudos anteriores sobre a concentração regional no desenvolvimento de tecnologia. No entanto, a nossa contribuição está em demonstrar esses fenômenos para vacinas contra a COVID-19 em subcontinentes e tecnologias específicas em nível nacional. Os nossos dados ressaltam quais subcontinentes realizam muito poucos ensaios clínicos para COVID-19 e parecem estar mal preparados para futuros surtos de doenças e no caso de esses se tornarem epidemias ou mesmo pandemias e exigirem desenvolvimento ou produção de vacinas domésticas. Consideramos também o caso do Brasil, que não encerrou o ciclo completo de desenvolvimento da vacina contra a COVID-19 no período indicado; mas, com políticas favoráveis, tem potencial para se envolver ainda mais na tecnologia de vacinas contra a COVID-19.

COVID-19; Vacinas; Desenvolvimento de Vacinas

Resumen

El propósito de este texto es reportar un análisis sobre la distribución global de instituciones involucradas en ensayos clínicos relacionados con vacunas del COVID-19 hasta febrero de 2022. Se recogieron datos globales de la Organización Mundial de la Salud sobre el desarrollo de vacunas; lo que se pudo identificar las instituciones del proyecto y rastrear sus coordenadas geográficas. Se elaboró un mapa georreferenciado utilizando el lenguaje de programación R y, a partir de la ubicación geográfica de los desarrolladores de vacunas, se analizó la distribución subcontinental de los ensayos clínicos y la naturaleza de las vacunas probadas. A nivel regional, los países del Sur Sureste Asiático llevaron a cabo proporcionalmente más ensayos clínicos que cualquier otra región, aunque esto se realizó con tecnologías consolidadas. Se registraron pocos ensayos en la etapa de implementación en América Latina y África. Los hallazgos confirman los estudios previos sobre la concentración regional en el desarrollo tecnológico. Sin embargo, permiten un aporte al demostrar estos fenómenos para vacunas contra el COVID-19 en subcontinentes y tecnologías específicas a nivel nacional. Los datos revelan los subcontinentes que realizan pocos ensayos clínicos para el COVID-19 y que no parecen estar bien preparados para futuros brotes de enfermedades, en caso de que se conviertan en epidemias o incluso pandemias, requiriendo el desarrollo o la producción de vacunas nacionales. Se considera también el caso de Brasil, que no completó el ciclo completo de desarrollo de la vacuna contra el COVID-19 en el periodo señalado; pero, con políticas favorables, tiene el potencial de involucrarse aún más en la tecnología de la vacuna del COVID-19.

COVID-19; Vacunas; Desarrollo de Vacunas

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