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Original Article

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The development of COVID-19 vaccines in the first year of the pandemic: a narrative study

O desenvolvimento de vacinas contra COVID-19 no primeiro ano da pandemia: um estudo narrativo

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Abstract

Introduction: in December 2019 a new disease emerged in Wuhan (China) and on March 11, 2020, the world began to witness the beginning of a pandemic that, for many, should not be feared; however, with the rapid spread of a totally unknown virus, the focus of health entities became the area of Research and Innovation, aiming at the production of an effective vaccine against COVID-19. **Objectives:** to present the vaccines under development, their testing and distribution during the first year of the pandemic in order to understand the path taken in the fight against the Coronavirus, as well as the increase in scientific production about this Emergency. **Materials and Methods:** this manuscript is based on a study of narrative mapping about vaccines for COVID-19 from March 11, 2020, to March 10, 2021. **Results:** in the first year of the pandemic, it was already possible to develop more than one vaccine, which was commercialized on a worldwide scale. In Brazil, vaccination began on January 18, 2021, when ANVISA approved the emergency use of CoronaVac, AZD1222 and COMIRNATY. **Conclusion:** in view of the above, the study of the development, testing and distribution of vaccines against COVID-19 during the first year of the pandemic was essential to understand the path traced in the fight against this disease.

Keywords: COVID-19; Coronavirus; vaccines; Treatment; Immunization.

Resumo

Introdução: em dezembro de 2019 uma nova doença surgiu em Wuhan (China) e em 11 de março de 2020 o mundo passou a presenciar o início de uma pandemia que, para muitos, não deveria ser temida; no entanto, com a rápida disseminação de um vírus totalmente desconhecido o foco das entidades de saúde passou a ser na área da Pesquisa e Inovação, visando a produção de uma vacina eficaz contra a COVID-19. **Objetivos**: apresentar as vacinas em desenvolvimento, além da sua testagem e distribuição, durante o primeiro ano de pandemia, a fim de entender o caminho traçado no combate ao Coronavírus, bem como o aumento da produção científica acerca dessa Emergência. **Materiais e Métodos**: o presente manuscrito se baseia num estudo de mapeamento narrativo sobre as vacinas para a COVID-19 no período de 11 de março de 2020 a 10 de março de 2021. **Resultados:** no primeiro ano de pandemia já foi possível o desenvolvimento de mais de uma vacina, as quais passaram a ser comercializadas numa escala mundial; no Brasil, a vacinação teve seu início em 18 de janeiro de 2021, tendo a ANVISA aprovado o uso emergencial da CoronaVac, AZD1222 e COMIRNATY. **Conclusão:** diante do exposto, o estudo acerca do desenvolvimento, testagem e distribuição das vacinas contra a COVID-19 durante o primeiro ano de pandemia é essencial para entender o caminho traçado no combate a essa doença.

Palavras-chave: COVID-19; Coronavírus; Vacinas; Tratamento; Imunização.

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Introduction

The COVID-19 pandemic is caused by the SARS-CoV-2 virus. This virus is a coronavirus that has reservoirs in animals belonging to the Coronaviridae family, which causes respiratory infections. The best known are SARS-CoV (which causes severe acute respiratory syndrome or SARS) and MERS-CoV (which causes Middle East respiratory syndrome or MERS), with the two alpha coronavirus subtypes HCoV-229E and HCoV- NL63 and the two beta coronavirus subtypes HCoV-OC43 and HCoV-HKU11. It is also worth noting that coronaviruses of α and β genera usually infect mammals and humans, while the coronavirus of the γ and δ genera mainly infect birds[2].

Despite a year studying this disease, researchers are still seeking the best therapeutic approaches to solve this crisis in the health system. At the beginning of the pandemic, in March 2020, antiviral agents such as ribavirin, favipiravir, remdesivir and galidesivir stood out as possible uses against SARS and MERS, because these agents act directly on interactions between cell receptors with the virus during encapsulation. Furthermore, they also highlight the possible use of similar nucleosides in adenine format or guanine derivatives, which act to block the synthesis of viral RNA in a wide spectrum of RNA virus, which would include human coronavirus[3].

With the Coronavirus, new care practices and ways of "doing health" emerged that were adapted to the conditions brought by this situation; however, there were still many challenges to be faced[4]. Thus, despite the various discussions about drugs to prevent and combat the New Coronavirus, the development of a vaccine was essential for its effective control. In this sense, there was a great worldwide movement towards the creation of a satisfactory vaccine, encompassing several different technologies, such as recombinant mRNA and inactivated-virus vaccines, and different stages of testing.

The word Vaccine is derived from the word *Variolae vaccinae* (cow pox), named by Edward Jenner to refer to cowpox[5]. In the 19th century, to honor Edward Jenner, the scientist Louis Pasteur suggested that the terms should be used to define new biological inoculations to human beings for the purpose of immunological protection[6]. Since then, vaccines have become more effective therapeutic forms of prevention against diseases such as Smallpox, Anthrax, Diphtheria, Measles, Mumps, Rubella, and Malaria[7]. In addition to their many advantages, vaccines are used to fight and eradicate infectious diseases, making them relevant to public health[8].

Vaccines are composed mostly of synthetic peptides, but we can find carbohydrates and antigens. There are eight different classifications of vaccines on the market: inactivated, attenuated, toxoid, subunit, conjugated, experimental, valence, and heterotypic. Furthermore, each type of vaccine undergoes a production and development method.

In short, the health crisis caused by the COVID-19 pandemic draws attention to the importance of science developed in the country and the need to strengthen incentives for the construction of scientific knowledge. Thus, a study was developed with the objective of describing the development, testing and distribution of vaccines against COVID-19 in the first year of the pandemic in order to understand the path taken in the fight against the Coronavirus, as well as the increase in scientific production about this Emergency.

Materials and Methods

The present manuscript was based the narrative mapping about vaccines for

COVID-19 in the first year of the pandemic. Thus, it is understood that narrative review studies are broad publications in which the materials used were analyzed in a generalized way and incorporated the work because they respond to the proposed objectives[9,10].

Thus, this methodology is appropriate to describe and discuss the development or 'state of the art' of a given subject, from a theoretical or conceptual point of view. The selection of materials is influenced by the authors' choice, according to the sources of information that are convenient for them to answer the research question. In this sense, this narrative review aims to build on the 'state of the art' of Covid-19 in its first year of the Pandemic, bringing together, for this purpose, various sources of information, whether from scientific or empirical results, materials published in databases of scientific journals, on government websites and/or institutions that guide health practices such as the World Health Organization (WHO) and the Pan American Health Organization (PAHO).

This research encompassed material published within the period of one year, between March 11, 2020 - when the WHO declared the new coronavirus pandemic - and March 10, 2021. Among the inclusion criteria, materials published in different languages in: articles, experience reports, editorials, documentaries, technical notes, epidemiological bulletins, and reports, and documentary, among others were included. Regarding the exclusion criteria, publications duplicated in different databases and materials, studies, works that did not meet the objective of this review were excluded.

For this research, the scientific bases SCIELO, LILACS, MEDLINE (BVS), PUBMED, COCHRANE and PERIODICOS CAPES were used. A total of 69 articles that addressed the theme were selected, and 15 of these were used in the study, from the descriptors Vaccine AND COVID-19. Databases such as the WHO's and other information vehicles such as news sites were also used.

Results

When a pandemic was declared, or even before that, researchers already knew that a vaccine against COVID-19 was the most efficient alternative to stop the spread of the virus. Soon, studies aimed at the production and testing of the vaccine began, not only studies on the creation of a totally new vaccine, but also the reuse of existing ones, such as BCG.

After the identification of the genetic sequences of SARS-CoV-2, in March 2020, the development of a vaccine became a global priority; as of March 2020, in December 2020, 198 vaccines had already been studied[11].

Also, the development of these vaccines focused on different technologies, as shown in Box 1.

Box 1. Technology used for the production of vaccines against COVID-19 in the first year of the Pandemic

Type of vaccine	How it works
Messenger RNA-based vaccines	An mRNA, containing an ORF, is first transcribed *in vitro* from a DNA template using an RNA polymerase. Then, the ORF encodes the protein of interest that serves as an antigen.
DNA vaccines	The DNA sequence is introduced into the cells of a specific tissue with a target sequence that generates a messenger RNA, which is encoded in viral surface protein production.
Live-attenuated virus vaccines	The viral genome is de-optimized to reduce its pathogenicity while maintaining its immunogenicity against multiple viral antigens.
Inactivated virus vaccines	Use of SARS-CoV-2 virion variants that are propagated through Vero (African Green Monkey) cell lines. After viral extraction, beta-propiolactone is used for inactivation with the viral particle, then adsorbed onto an adjuvant (aluminum hydroxide).
Protein subunit vaccines	Based on synthetic peptides or recombinant proteins of the target

	pathogen. *Spike* protein (S) is the main target antigen, in addition to nucleocapsid protein (N) and membrane protein (M).
Recombinant viral vector vaccines	A non-pathogenic virus is used to produce Coronavirus antigens

Source: own elaboration based on Arora and Manoja[12], Ferraz, Mendes and Von Der[13], Frederiksen et al.[14], Izda, Jeffries and Sawalha[15], Marian[16] and Ong et al[17].

Furthermore, in the development of a new vaccine, the study must go through three phases before making it available, which is consecrated as the fourth phase, as described in Box 2.

Box 2. Phases of the clinical trial for the development of a new vaccine.

Phase I	**It evaluates the safety of the vaccine. A small number of healthy volunteers (<100) is needed.**
Phase II	It evaluates the immunogenicity of the vaccine. A larger number of volunteers with the pathology is needed (200-500).
Phase III	It evaluates the effectiveness of the vaccine. Randomized, double-blind, placebo-controlled study.
Phase IV	Vaccine made available to the population.

Source: own elaboration based on Ferraz, Mendes and Von Der[13] and Quental and Salles Filho[18].

Despite international efforts to create an effective vaccine by 2020, countries had not reached an agreement on which among the vaccines under development were the most effective. Thus, in February 2021, at least 7 vaccines were internationally approved, but in the following month, there were still several vaccines in development, especially those that were in clinical trial, as shown in Box 3.

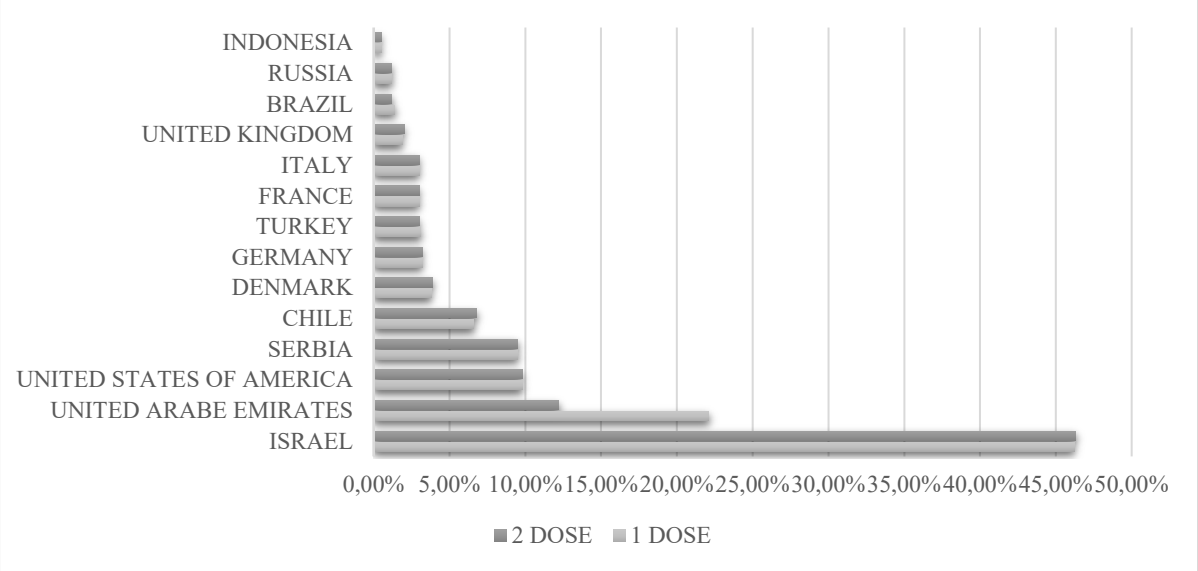
Box 3. Candidate vaccines for COVID-19 in clinical trial in March 2021.

Platform	Number of candidate vaccines
Protein subunit	27
Viral vector (no replication)	12
DNA	11
inactivated virus	11
RNA	10
Viral vector (replicant)	4
Virus-like particle	3
VVr+ antigen presenting cell	2
Live-Attenuated Virus	1
VVnr+ antigen presenting cell	1

Source: own elaboration based on WHO[19].

The discrepancy in the vaccination process at the international level was also noticeable. While the United Kingdom started the immunization process on December 8, 2020, Brazil only started on January 18, 2021. This divergence in the number of people vaccinated in the different countries can be seen in Figure 1.

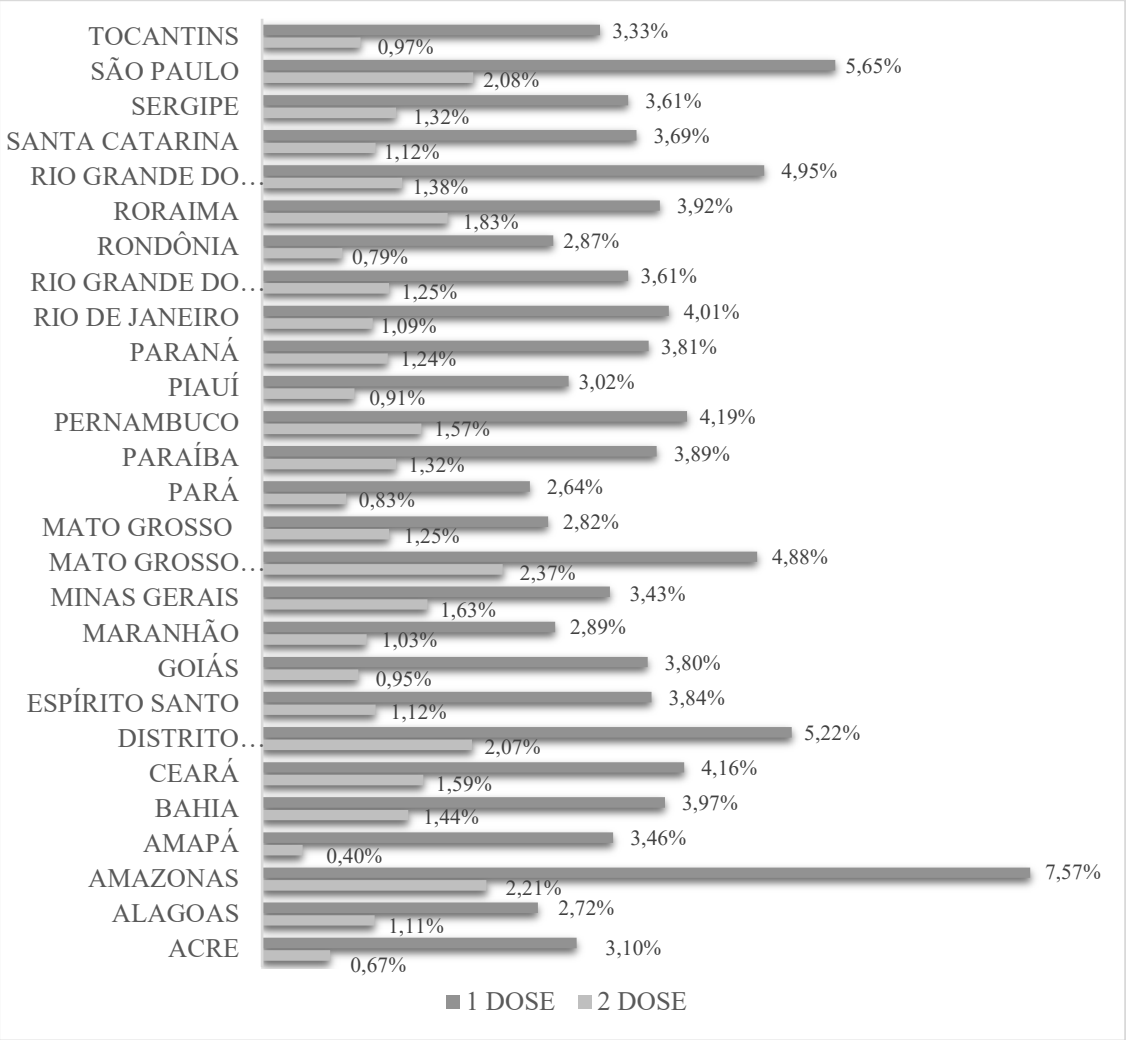
Figure 1. 1st and 2nd doses of vaccines against COVID-19 administered per country until 03/10/2021.



Source: own elaboration based on OperaMundi[20].

This divergence was also present at the national level, as shown in Figure 2.

Figure 2. Nationally administered vaccine doses up to 03/10/2021.



Source: own elaboration based on G1[21].

Discussion

With the emergence of the New Coronavirus, the world's scientific population began to move towards the development of an effective method of combat, with the vaccine being the most desired. Thus, it was possible to observe the movement and global alliances in the first year of the pandemic aimed at this development, and even after some vaccines being approved for use, clinical trials continued to be performed with others. Never in history had a vaccine been developed so fast as the vaccine against COVID-19. As soon as in the first year, the population saw the beginning of vaccinations, although not in a comprehensive and homogeneous way. The difference in the immunization process was noticeable both at the national and international levels, a fact demonstrated by the data presented by national and international bodies on the number of doses administered in a given period of time.

In a brief analysis of studies on effective vaccines against COVID-19 in 2020, it is possible to note that at the beginning of the pandemic, China took the lead in the development of the vaccines, and countries such as the United States of America and Russia were close behind. However, as of May 2020, 46% of vaccines in progress were already being developed in North America, while 18% were being developed in China[22]. However, there was no way for researchers and world leaders to know which country would release its vaccine first, which triggered sociopolitical alliances and disagreements.

The desire for a new vaccine can be observed in the number of existing studies since March/April 2020. At the beginning of April, there were 115 candidate vaccines, 78 of which were confirmed as active and of these 73 were already in the exploratory or pre-clinical phase, with the main ones being mRNA-1273 from Moderna, Ad5-nCoV from CanSino Biologicals and including INO-4800 from Inovio[22]. At the beginning of May, the numbers dropped to 108, of which 100 were in pre-clinical phases, while 8 of them were in clinical phases 1 or 2[12]. In July, WHO data[19] showed the existence of 137 vaccines in pre-clinical development and 23 in initial clinical development, while in August, 250 candidate vaccines were registered, with at least 17 in clinical trials[23].

Following this line, in the month of September, there were 180 candidate vaccines, 42 of which were in clinical trials[24]. In November, 53 vaccines were analyzed, evaluated in 126 clinical trials in 35 countries, of which 12 were in phase III trials, highlighting the vaccines from BioNTech (BNT162b2), from Moderna (mRNA 1273), from the University from Oxford (AZD1222), from Russia (Sputnik V), and Ad5-nCoV and CoronaVac, from China[25]. At the end of the year, in December 2020, there were 198 candidate vaccines for COVID-19, comprising 44 in clinical trials[11].

Also, in October 2020, there was a study on the amount of vaccines that had been developed according to each technology[26]. Regarding vaccines from recombinant viral vectors, the researchers mentioned the existence of 4 candidates in clinical trials, 38 in pre-clinical trials, and the vaccines ChAdOx1 nCoV-19 (AstraZeneca/University of Oxford), Ad26-S (Johnson & Johnson) and VSV-S had been selected for the US Operation Warp Speed (public-private partnership for further vaccine development initiated in the United States of America). Regarding inactivated vaccines, 9 were in pre-clinical development, with the PiCoVacc vaccine (Sinovac Biotech Ltd) being the most advanced, with published pre-clinical results. In terms of protein subunit vaccines, the authors state that there were 7 in clinical trials and 50 in the pre-clinical

phase, with emphasis on the NVX CoV2373 vaccine (Novavax Inc.).

As for mRNA-based vaccines, there were 6 in clinical trials and 16 in pre-clinical trials, notably BNT162b2 (BioNTech/Pfizer) and mRNA 1273 (Moderna)[25]; while there were 4 DNA-based vaccines in the clinical phase and 11 in the pre-clinical phase. Furthermore, there were 20 non-replicating viral vector vaccines under development in November, 2020, of which 8 were in the clinical phase[24].

In 2021, there was still a strong need for a vaccine, so as of February 18, at least 7 vaccines worldwide were approved for emergency use, concomitantly with the development of another 200 candidate vaccines[19]. In this context, in March 2021, WHO[19] published the existence of 182 vaccines in pre-clinical trials and 82 in clinical trials.

On December 8, 2020, the United Kingdom started vaccinating its inhabitants with the Pfizer/BioTech vaccine, being the first country to start the process, and on the 24th of the same month, 56 other countries had also started vaccination[27]. In Brazil, vaccination began on January 18, 2021, with the priority groups of phase 1, after the approval by ANVISA of the emergency use of CoronaVac (developed by Sinovac and the Butantan Institute) and AZD1222 (developed by AstraZeneca, Oxford University and Fiocruz)[28]. On February 23, 2021, ANVISA also granted definitive registration to the COMIRNATY vaccine (developed by Pfizer and BioNTech), however, it was to be used from the second half of 2021[29].

Although vaccination had already started in several countries, this immunization process was not homogeneous. It was noticeable that countries that were in the lead in the development of the vaccine as well as countries with strong leaders who supported the measures indicated by the World Health Organization since the beginning are now in a better context of immunization and combat against the Coronavirus. In turn, countries that discredited the effectiveness of vaccines or more marginalized countries go through a much slower process of vaccination, dealing with a greater disorganization of the system, as well as the lack of vaccines in the units and lack of inputs for the production of new vaccines, as is the case of Brazil.

In this context, when analyzed internationally until the period of March 10, 2021[20], Israel's leadership in vaccinating its population was perceptible, having equalized the number of the first and second doses administered, bringing data of 46.30% of the population already vaccinated, well ahead of the United States, which had only 9.80% of its population immunized. When these data were compared with Brazil, there was a great divergence, since the country had applied the first dose to only 1.4% of the population and the second to 1.20%.

Regarding the national data, certain divergences in immunization between states were also found. Until March 10, 2020[21], the highest vaccination rates were found in the state of Amazonas, with 7.57% of people having received the first dose, but only 2.21% having received the second. Next, the state of São Paulo stood out with 5.65% having received the first dose and 2.08% having received the second. The lowest vaccination rates were from the states of Pará (2.64% for the first dose and 0.83% for the second) and the state of Alagoas (2.72% for the first dose and 1.11% for the second dose). In the analysis by regions, the Southeast region had the highest percentage (4.23%) in relation to the first dose and the Midwest had the lowest (3.83%), as for the second dose, the Midwest region had the highest percentage (1.52%) and the North region had the lowest (1.1%).

Conclusion

From the emergence of an unknown disease and based on the resumption of crises and pandemics in history, international agencies and universities began to accelerate and generate greater visibility for their scientific performance. The desire and need for an effective vaccine against the coronavirus led global organizations to work in an accelerated way for this search, which was also able to show the impact generated by the incentive to Research in the most diverse countries, as well as the positive or negative impact about respect for the preventive standards imposed by the World Health Organization.

Thus, with the COVID-19 pandemic, declared on March 11, 2020, by the World Health Organization, the creation of a vaccine against this virus was sought. Since March 2020, several places have started to study how this vaccine could be developed; in December 2020 there were 198 vaccines in development and in March 2021, despite the use of some vaccines at the same time around the world, WHO data showed the existence of 82 vaccines in clinical trials.

In this sense, researchers managed to create a vaccine in the shortest time in history and unite nations. In Brazil, 3 vaccines were approved for emergency use by ANVISA, namely CoronaVac (Sinovac/Instituto Butantan), AZD1222 (AstraZeneca/University of Oxford/Fiocruz) and COMIRNATY (Pfizer/BioNTech). Despite the beginning of the immunization, the national and international heterogeneity of this process is remarkable, based on the study of the number of people vaccinated in each country and, at the national level, in each state.

Furthermore, the pandemic brought an emergency character to the field of health and, at the same time, brought to light problems and vulnerabilities in the most diverse social and economic areas. In this context, there was greater solidarity in the community and a disparity between government officials who, on the one hand, followed WHO standards and believed in science and, on the other hand, chose to discredit research.

In short, the COVID-19 pandemic openly exposed the vulnerability of the health field and highlighted the importance of investment in science, research and innovation, bringing lessons that cannot fail to be observed and incorporated into State policies**.**

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