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Regulatory reliance pathways during health emergencies: enabling timely authorizations for COVID-19 vaccines in Latin America

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ABSTRACT

Objectives. To map the timing and nature of regulatory reliance pathways used to authorize COVID-19 vaccines in Latin America.

Methods. An observational study was conducted assessing the characteristics of all COVID-19 vaccine authorizations in Latin America. For every authorization it was determined whether reliance was used in the authorization process. Subgroups of reference national regulatory authorities (NRAs) and non-reference NRAs were compared.

Results. 56 authorizations of 10 different COVID-19 vaccines were identified in 18 countries, of which 25 (44.6%) used reliance and 12 (21.4%) did not. For the remaining 19 (33.0%) it was not possible to determine whether reliance was used. Reference agencies used reliance less often (40% of authorizations with a known pathway) compared to non-reference agencies (100%). The median review time was just 15 days and does not meaningfully differ between reliance and non-reliance authorizations.

Conclusions. This study demonstrated that for these vaccines, despite reliance pathways being associated with numerous rapid authorizations, independent authorization review times were not considerably longer than reliance reviews; reliance pathways were not a prerequisite for rapid authorization. Nevertheless, reliance pathways provided rapid authorizations in response to the COVID-19 emergency.

Keywords Regulatory frameworks; COVID-19; health priorities; Latin America; global health; drug approval; COVID-19 vaccines; drug utilization review.

Ensuring timely access to novel medicines for people in low- and middle-income countries (LMICs) is an ongoing challenge (1,2). The COVID-19 pandemic made this issue more prominent than ever by creating an unprecedented demand for novel vaccines worldwide, resulting in several vaccines being developed in record time. Like the rest of the world, Latin American countries were struck by serious COVID-19 outbreaks (3) and thus needed to have timely vaccine authorizations by their national regulatory authorities (NRAs) in order to combat the pandemic. The length of these authorization processes thus directly influenced how quickly novel vaccines could be administered to the population. This meant that, like COVID-19 vaccine development, the regulatory review and authorization process also had to be expedited significantly. This posed a particular challenge for LMICs, including those in Latin America, since many have under-resourced NRAs

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that lack the regulatory tools and expertise to deal with health emergencies (4,5).

Despite this, countries in Latin America were able—with varying degrees of success—to expedite their review processes and rapidly authorize multiple vaccines (6). Expediting such regulatory review processes is typically achieved through the use of Facilitated Regulatory Pathways (FRPs): regulatory pathways designed to accelerate regulatory submissions and reviews (7). Well-known examples of FRPs are EMA's accelerated assessment and Conditional Market Approval, and FDA's Breakthrough Therapy designation and priority review. FRPs function through a variety of methods such as accelerating review times, increased agency-sponsor interaction, rolling reviews, and applying reliance mechanisms (7). Reliance pathways especially are considered vital to providing people in LMICs timely access to novel medicines (7–9). They allow NRAs to rely on the regulatory efforts of their counterparts in reference countries, thereby reducing duplication of effort and enabling NRAs to optimize review times while focusing on other added-value activities. Additionally, practicing reliance enables maturing NRAs that lack the resources to train or hire those able to assess increasingly complex medicines to nevertheless make informed, sovereign regulatory decisions (8).

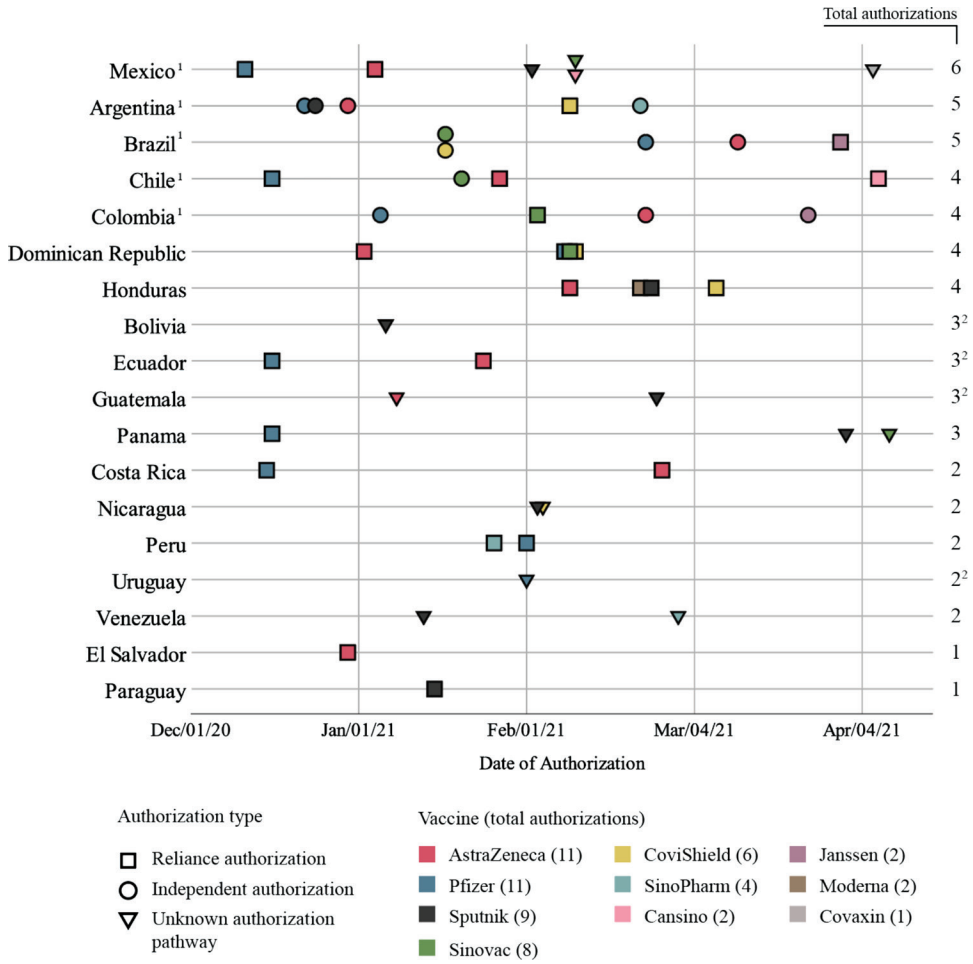
Sixty-five percent of Latin American NRAs were found to have reliance pathways in place as of June 2020 (10). However, the role of reliance pathways in the rapid emergency authorizations of COVID-19 vaccines has not been well documented. An analysis of this landscape could inform NRAs that do not have formal pathways for health emergencies or special cases. Furthermore, an increased understanding of these mechanisms could identify common and best practices that could help to optimize regulatory processes in LMICs outside of emergency situations (11), especially processes regarding innovative products that address a high unmet medical need (12).

Therefore, this study was conducted to map the timing of and use of reliance in the regulatory pathways used to authorize COVID-19 vaccines in Latin America.

METHODS

To assess the timing and use of reliance pathways to authorize COVID-19 vaccines in Latin America, we conducted an

FIGURE 1. Timeline of COVID-19 vaccines authorizations in Latin America



Note: Each COVID-19 vaccine authorization in Latin America with a known authorization date (n=51) is shown as a symbol on the timeline. The location of the symbol indicates the date and country of an authorization. The colour and shape of the symbol indicate what vaccine was authorized, and whether the authorization was independent, used reliance, or used an unknown pathway.
[1] PAHO regional reference NRA.
[2] Authorization(s) with missing authorization date not shown.

observational study of past authorizations. To assess variations within the region itself, a comparison between Pan American Health Organization (PAHO) regional reference NRAs and non-reference NRAs was performed. PAHO regional reference NRAs are those at the highest level of maturity (level 4) according to an assessment by PAHO. They are competent in their performance of health regulation functions, serve as reference to other NRAs in Latin America, and support reliance (9). We used the agency descriptor of the pathway, categorizing the pathway based on the documentation indicating that reliance was used. In the absence of a formal agency statement, we applied the World Health Organization (WHO) definition of reliance to categorize pathways.

A database was constructed of Latin American COVID-19 vaccine authorizations that occurred up to April 16, 2021. Authorizations were identified using trackvaccines.org and reuters.com. Additionally, every country was reviewed individually through Google web searches consisting of the country name combined with search terms relevant to vaccine authorizations (being 'vaccine', 'emergency use', 'approved', and 'approval' along with their Spanish and Portuguese translations) and the names of all known COVID-19 vaccines and vaccine manufacturers. Periodic information alerts provided by PAHO were also reviewed to determine vaccine authorization status.

After an authorization was identified, the websites of the corresponding NRA and Ministry of Health were systematically searched for government notices or similar news-like pages regarding the authorization by manually reviewing pages published on or around the date of authorization and through the search functionality provided by the websites. DeepL translator (deepl.com, version 1.17.1 to 2.4.0) was used to translate Spanish and Portuguese pages and the legislation to which they referred; translation clarifications were provided by a Spanish and Portuguese speaking author. Additionally, reuters.com articles regarding the authorization were collected using the same search terms used for authorization identification. These articles were reviewed for supplemental information about the legislation behind an authorization that was not published on government websites. In case a country assessed the same vaccine twice (e.g., emergency authorization and full approval) only the first authorization of the vaccine was included in the database.

The compiled data was used to determine a consistent set of characteristics for each authorization. Characteristics included date of submission, date of authorization, and relevant legislation (i.e., laws, decrees, resolutions). Additionally, all authorizations were classified as either *reliance-, independent-, or unknown pathway authorizations.* For authorizations of which the applied legislation was known, it was determined whether the NRA applied a reliance pathway as per the WHO definition of reliance (The act whereby the NRA in one jurisdiction may consider and give significant weight to—i.e., totally, or partially rely upon—evaluations performed by another NRA or trusted institution in reaching its own decision). The relying authority remains responsible and accountable for decisions taken even when it relies on the decisions and information of others to grant authorization (*reliance authorizations*), or if the authorization was not dependent on prior reference decisions (*independent authorizations*). Authorizations for which no information on the applied pathway was available were considered *unknown pathway authorizations*; in these cases, it was not possible to determine whether reliance mechanisms were or were not used. Before analysis, data were shared with 11 Latin American NRAs and with Pfizer, AstraZeneca, and Janssen for verification, resulting in 4 replies with 8 additions and 2 corrections, of which 9 involved authorization/submission dates and one added a known reliance pathway.

A descriptive analysis of the number of authorizations per country, the prevalence of the use of reliance pathways, and review times was performed using IBM SPSS Statistics (Version 26.0. Armonk, NY: IBM Corp). Comparisons between the subgroups of reference and non-reference NRAs were made via the same process.

RESULTS

Fifty-six authorizations of 10 different COVID-19 vaccines were identified in 18 Latin American countries (Figure 1). Of these, 25 (44.6%) used a formal reliance pathway and 12 (21.4%) authorizations were not dependent on a prior reference decision. The remaining 19 cases (33.9%) were considered unknown pathway authorizations since no information about the applied procedure was publicly available. Importantly, reliance approaches were used by 13 of the 18 countries (72.2%) of the countries, encompassing both reference and non-reference agencies.

Besides the wave of Pfizer authorization in mid-December, no obvious patterns are visible in the timeline. Some countries authorized multiple vaccines in short timespans (e.g., Honduras), while others had months-long intervals between authorizing vaccines (e.g., Panama and Costa Rica).

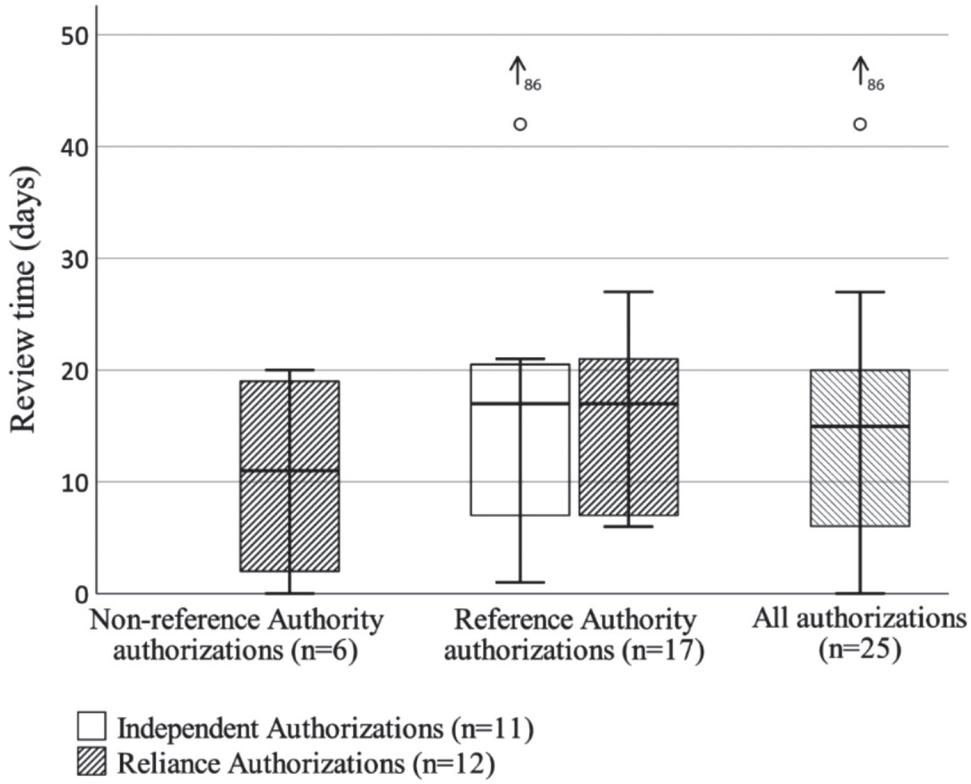
A comparison of PAHO regional reference and non-reference NRAs in terms of COVID-19 vaccines authorizations identified differences in the number of authorizations and the use of reliance. Non-reference authorities authorized fewer vaccines on average and more often applied reliance compared to reference authorities. (Table 1). All authorizations by non-reference NRAs of which the applied legislation was known used reliance (53.1%, n=17); however, no independent authorizations by non-reference agencies were identified. Non-reference NRAs more often had unknown pathway authorizations. Table 1

TABLE 1. Characteristics of COVID-19 vaccine authorizations by reference and non-reference NRAs in Latin America

	Average number of authorizations per country	*Total authorizations*	*Reliance authorizations (% of total)*	*Independent authorizations (% of total)*	*Unknown pathway authorizations (% of total)*
Reference NRAs (5)	4.8 (SD .84)	24	8 (33.3%)	12 (50.0%)	4 (16.7%)
Non-reference NRAs (13)	2.5 (SD .94)	32	17 (53.1%)	0 (0%)	15 (46.9%)
Total	3.1 (SD 1.41)	56	25 (44.6%)	12 (21.4%)	19 (33.9%)

NRA, National Regulatory Authority

FIGURE 2. Clustered boxplot diagram showing COVID-19 vaccine review times of reference and non-reference authorities in Latin America by authorization type



Note: Review time equals the number of days between submission date and the authorization date. Review times of two unknown-pathway authorizations only present under 'all authorizations'.

provides an overview of the differences between reference and non-reference authorities.

The review time (i.e., number of days between submission date and authorization date) of 25 authorizations (44.6% of total) in 11 countries was identified; the review times for the remaining 31 authorizations were not known due to unknown submission or authorization dates. The median review time of these authorizations was 15 days (IQR 14). Review times did not meaningfully differ when comparing reliance (median 16 days) and non-reliance authorizations (median 17 day) or when comparing authorizations by reference (median 16 days) and non-reference authorities (median 14 days) (Figure 2).

DISCUSSION

The COVID-19 response prompted unprecedented levels of regulatory agility (13) and an unprecedented number of vaccines being authorized in record time around the globe. Latin American countries were able to rapidly authorize novel COVID-19 vaccines through both reliance and authorization pathways independent from prior authorization decisions. 56 authorizations of 10 different COVID-19 vaccines were identified in 18 countries, of which 25 (44.6%) used reliance and 12 (21.4%) authorizations did not. Reference agencies used reliance less often (40.0% of authorizations with a known pathway) compared to non-reference agencies (100%). The median review time was just 15 days and did not differ meaningfully between reliance and non-reliance authorizations.

Yet, independent authorization review times were not considerably longer (median 17 days). Thus, despite reliance pathways being associated with numerous rapid authorizations by mostly non-reference NRAs, they did not appear to be a prerequisite for timely authorizations in response to a pandemic. Considering the median review time for new molecular entities in Latin America was found to be 420 days (14) and vaccines generally take years to get widespread authorization in LMICs (1), independent authorizations were also accelerated substantially in response to the pandemic need, albeit through other means than formal reliance.

From a public health perspective, these findings indicate that reliance pathways can facilitate authorizations especially among less well-resourced agencies but that more well-resourced reference agencies are able to re-prioritize their activities to accommodate non-reliance-dependent procedures that can match the timeliness of reliance pathways. However, this reprioritizing could have (and likely has had) a knock-on effect on delaying the review of previously submitted applications, which have remained unaddressed during the period in which resources have been re-allocated. Despite this, preceding authorizations in other countries may still have played a role in their acceleration, which could be considered a form of informal reliance.

The high prevalence (44.6%) of reliance authorizations and their short review times (median 16 days) demonstrate that reliance pathways can provide rapid authorizations in response to emergencies like COVID-19. We observed that 80.0% of the

approvals were through an Emergency Use Authorization (Brazil and Peru used a conditional marketing authorization) and these approaches likely contributed to accelerating the authorization process.

The clustering of reliance and unknown pathway authorizations in non-reference countries may be influenced by non-reference NRAs generally being more resource restricted and less transparent in reporting the nature of the pathways used compared to reference NRAs (15), since resource limitations incentivize reliance on others (16), and a lack of transparency is associated with a limited amount of publicly available data about the applied pathway (15). All authorizations in non-reference countries of which the applied pathway was known used reliance; hence, it might be expected that some or even most of the unknown pathways used by non-reference NRAs were also reliance pathways, especially given that most Latin American countries already had reliance pathways in place (10). This is consistent with PAHO's ambitions for reliance in the region, wherein non-reference NRAs are able to rely on reference agencies (9).

The limited amount of publicly available data for some authorizations was the primary limitation of this study. This is reflected in the number of unknown pathway authorizations in mostly non-reference countries, for which the regulatory pathway used could not be identified. This may bias the results towards countries with more mature NRAs, since those tended to be more transparent in reporting their processes. The existence of a legislated reliance route is no guarantee of its use in practice; however, our observation of the use of reliance approaches by 72.2% of the countries evaluated strongly suggests that there was a recognition of the value of this approach in this cohort of agencies. We attempted to address this by contacting drug sponsors and NRAs for data verification. However, not all vaccine sponsors could be contacted and not all those contacted responded. Thus, vaccines whose sponsors did respond are slightly overrepresented in review-time analysis because of them providing more comprehensive data. Data collection ending on April 16th meant at least 28 authorizations were excluded from this analysis since 84 authorizations were given in Latin America as of October 2021 while 56 were included in this study.

While the COVID-19 vaccine experience optimized the pandemic readiness of NRAs, a challenge lies in extending these successes beyond emergencies alone. Despite it being unrealistic to expect LMIC NRAs to treat all novel medicine as urgently as COVID-19 vaccines, the regulatory agility shown by NRAs during the pandemic is expected to be at least partially transferable to non-emergency situations (11). This could enable under-resourced NRAs to conduct their regulatory activities more efficiently, especially activity concerning innovative products that address a high unmet medical need (e.g., oncology products, advanced therapy medicinal products, novel vaccines).

Conclusions

This observational study was conducted to map the timing of and use of reliance in the regulatory pathways used to authorize COVID-19 vaccines in Latin America.

For these vaccines, despite reliance pathways being associated with numerous rapid authorizations, independent authorization review times were not considerably longer than reliance reviews; reliance pathways were not a prerequisite for rapid authorization.

Nevertheless, reliance pathways provided rapid authorizations in response to the COVID-19 emergency. Learnings from the COVID-19 authorization experiences should provide agencies and companies with the opportunity to identify ways to optimize regulatory strategies especially where a serious or unmet medical needs exists. To distil learnings from these rapid authorizations, a better understanding of how the pathways that enabled them were applied or modified to meet the demands set by COVID-19 is crucial and would enable this pandemic response to become a catalyst for positive regulatory change in NRAs worldwide. Therefore, we expect that learnings from this experience could be translated in part to non-pandemic scenarios to address unmet medical needs and broader public health crises.

Author contributions. ITVDZ: study design, data collection, data analysis, data interpretation; RV: study design, methodology, data analysis, data interpretation, supervision; LL: methodology, data collection, verification of data analyses; MAG: data collection, verification of data analyses. All authors were involved in the writing of the manuscript and reviewed and approved the final version.

Conflict of interests. None declared. RV is part-time employee of the Dutch National Health Care Institute, unrelated to this study.

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Mecanismos de utilización de las decisiones de autoridades regulatorias de otras jurisdicciones en las emergencias de salud: autorización oportuna de las vacunas contra la COVID-19 en América Latina

RESUMEN

Objetivos. Determinar dónde y cuándo se usaron las decisiones de autoridades regulatorias de otras jurisdicciones y la naturaleza de estos mecanismos para autorizar vacunas contra la COVID-19 en América Latina.
Métodos. Se realizó un estudio observacional para evaluar las características de todas las autorizaciones de vacunas contra la COVID-19 en América Latina. Para cada autorización se determinó si se emplearon las decisiones de autoridades regulatorias de otras jurisdicciones en el proceso de autorización. Se compararon subgrupos de autoridades regulatorias nacionales (ARN) consideradas de referencia con otras ARN no usadas como referencia.
Resultados. Se determinó dónde se otorgaron 56 autorizaciones de 10 vacunas diferentes contra la COVID–19 en 18 países; de estas 56 autorizaciones, 25 (44,6%) hicieron uso de las decisiones de autoridades regulatorias de otras jurisdicciones y 12 (21,4%), no. Para las 19 restantes (33,0%) no fue posible determinar si se hizo uso de las decisiones de autoridades regulatorias de otras jurisdicciones. Los organismos de referencia utilizaron las decisiones de autoridades regulatorias de otras jurisdicciones con menos frecuencia (40% de las autorizaciones con un mecanismo conocido) en comparación con los organismos no usados como referencia (100%). El plazo medio de revisión fue de tan solo 15 días y no difiere significativamente entre las autorizaciones que emplearon decisiones de autoridades regulatorias de otras jurisdicciones y las que no las emplearon.
Conclusiones. En este estudio se demostró que, a pesar de que los mecanismos de utilización de las decisiones de autoridades regulatorias de otras jurisdicciones se asocian en muchos casos con autorizaciones rápidas, para estas vacunas los plazos de revisión independiente para la autorización no fueron considerablemente mayores que los de las revisiones que emplearon decisiones de autoridades regulatorias de otras jurisdicciones. También se demostró que para obtener una autorización rápida no se requería la utilización de las decisiones de autoridades regulatorias de otras jurisdicciones. Sin embargo, estos mecanismos proporcionaron autorizaciones rápidas en respuesta a la emergencia por la COVID–19.

Palabras claves Marcos reguladores; COVID-19; prioridades en salud; salud global; aprobación de drogas; vacunas contra la COVID-19; revisión de la utilización de medicamentos.

Uso de decisões regulatórias de outras autoridades durante emergências sanitárias e a tempestividade da autorização de vacinas contra a COVID-19 na América Latina

RESUMO

Objetivos. Mapear a tempestividade e a natureza do uso de decisões regulatórias de outras autoridades (*reliance* regulatório) para autorização de vacinas contra a COVID-19 na América Latina.
Métodos. Em um estudo observacional, foram avaliadas as características de todas as autorizações de vacinas contra COVID-19 na América Latina. Para cada autorização, foi determinado se foram utilizadas decisões de outras autoridades regulatórias para embasar o processo de autorização. Foram comparados subgrupos de autoridades reguladoras nacionais (ARN) de referência (ARNr) e ARN não consideradas de referência.
Resultados. Foram identificadas 56 autorizações de 10 vacinas diferentes contra a COVID-19 em 18 países, das quais 25 (44,6%) utilizaram decisões de outras ARN como base para o registro e 12 (21,4%) não. Para as 19 (33,0%) autorizações restantes, não foi possível determinar se decisões de outras ARN foram utilizadas. As ARNr utilizaram decisões de outras autoridades com menos frequência (40% das autorizações com via regulatória conhecida) em comparação com as ARN não consideradas de referência (100%). A mediana do tempo de tramitação foi de apenas 15 dias, sem diferença significativa entre processos nos quais foram utilizadas decisões de outras agências e processos que não as utilizaram.
Conclusões. Este estudo demonstrou que, para estas vacinas, apesar de o uso do *reliance* regulatório estar associado a várias autorizações rápidas, os tempos de tramitação não foram consideravelmente maiores em autorizações independentes do que quando foram utilizadas decisões de outras ARN; o *reliance* regulatório não foi um pré-requisito para autorização rápida. No entanto, o uso de tais processos viabilizou autorizações rápidas em resposta à emergência de COVID-19.

Palavras-chave Marcos regulatórios; COVID-19; prioridades em saúde; saúde global; aprovação de drogas; vacinas contra COVID-19; revisão de Uso de medicamentos.