Major research project report

Ivar van der Zee

5693225

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Supervisors:

Rick Vreman, Utrecht University

Lawrence Liberti, Temple University

Mario Alanis, Centre for Innovation in Regulatory Science

Examiner:

Aukje Mantel-Teeuwisse, Utrecht University

General Introduction

Here we are, 9 months after I joined the Division Pharmacoepidemiology & Clinical Pharmacology for my major research project of which the resulting 2 research papers are presented in this document. The first provides a very practical angle on how reliance pathways were used to authorize vaccines in response to the COVID-19 pandemic. The second takes a step back by providing a more critical view towards the impacts of reliance, hereby offering some perspective on the first project. They represent a large part of what kept me busy during a year of working from home and I hope the papers convince some that there are interesting sides to even something as seemingly dull as regulatory affairs. Lastly, I would like to thank my supervisors Rick, Larry, and Mario, for their contributions, guidance, insightful ideas, and our discussions every Tuesday afternoon. They always provided a nice way to debate ideas, brainstorm, argue, or talk about the weather.

Layman's summary

Before a newly developed drug is authorized to be used within a country, the drug national regulatory authority (NRA) of that country (e.g., America's Food and Drug Administration) must assess whether a drug is both safe and effective. This is a costly process for NRAs that can take more than a year to complete. To reduce the time and resources spend on these assessments, NRAs sometimes make use of the work done by other NRAs that they trust. After all, why would every country separately spend the time and resources to assess the same drug if they could just rely on the work of a trusted other country? This act of one country's NRA using work done by another country's NRA to inform its own decisions is called *reliance*. Reliance is the overarching theme of the studies presented in this document, both of which are summarized below.

The first study assesses how Latin-American NRAs used reliance to rapidly authorize COVID-19 vaccines in response to the pandemic despite generally being less well-resourced than, for example, US or European NRAs. This is important to know since there is likely something to be learned from their pandemic response that can be used to speed up authorizations outside of pandemics, which would give people faster access to novel medicine. For every COVID-19 vaccine authorization granted in Latin-America we determined whether reliance was used and how long the NRA took to complete its assessment and grant authorization. Of the 56 authorizations, 45% used reliance and 21% did not, for the remaining 34% we could not determine whether reliance was used. Within Latin-America, less well-developed NRAs (e.g., El Salvador, Paraguay) used reliance more often than well-developed NRAs (e.g., Mexico, Brazil). NRAs needed just 16 days on average to assess COVID-19 vaccines, which is very fast. However, the time to assess vaccines did not differ between authorizations that used reliance and authorizations that did not. This shows that while reliance can enable very quick authorizations, it is not a prerequisite.

The second study in this document addresses the issue that it is often unclear what the exact consequences (or impacts) are when an NRA decides to start using reliance. While reliance is often written about as if it is always a good solution, the exact consequences of using reliance for a country's public health, economy, or its NRA are not well understood and have never been measured. This is a problem since it limits the ability of NRAs to know whether they should start using reliance, or if their current reliance activities are beneficial to them. To address this, we propose a way to assess the return-on-investment of using reliance called "Relianomics". As a starting point for this new approach, we analyzed literature that discusses reliance to create a categorized overview of things that are possibly impacted by using reliance. While developing Relianomics further will require a lot more time and resources, we believe the investment is worth it and think that a Relianomics is needed for better understanding how NRAs can effectively use reliance.

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

Abstract

Background: Latin American countries had to rapidly authorize COVID-19 vaccines in response to the pandemic. A common mechanism for NRAs to expedite authorizations is through relying on trusted NRAs from other jurisdictions (i.e., regulatory reliance). The use of reliance within vaccine authorizations is not known. Therefore, this study mapped 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 NRAs and non-reference NRAs were compared.

Results: 56 authorizations of 10 different COVID-19 vaccines were identified in 18 countries, of which 25 (45%) used reliance and 12 (21%) authorizations did not, for the remaining 19 (34%) 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 reliance pathways can provide rapid authorizations in response to emergencies like COVID-19. Yet, independent authorization review times were not considerably longer. Thus, despite reliance pathways being associated with numerous rapid authorizations, they are not a prerequisite.

Introduction

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

Despite this, countries in Latin America were—with varying degrees of success—able 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).

65 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, an observational study of past authorizations was conducted. 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 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). Reliance is defined according to the World Health Organization (WHO) definition, provided in Box 1.

Data Collection

A database was constructed of Latin American COVID-19 vaccine authorization 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 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.

Box 1: 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."

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 was used to translate Spanish pages and the legislation to which they referred; translation clarifications were provided by a Spanish 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 & 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 (Box 1) 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 1 added a known reliance pathway.

Analysis

A statistical descriptive analysis of the number of authorizations per country, the prevalence of the use of reliance pathways, and review times was performed using SPSS. Comparisons between the subgroups of reference and non-reference NRAs were made via the same process.

Results

56 authorizations of 10 different COVID-19 vaccines were identified in 18 Latin American countries (Figure 1). Of these, 25 (45%) used a formal reliance pathway and 12 (21%) authorizations were not dependent on a prior reference decision. The remaining 19 cases (34%) were considered unknown pathway authorizations since no information about the applied procedure was publicly available. An overview of authorization characteristics is provided in Table 1. Figure 1 provides a detailed timeline of all countries, vaccines, authorization dates and authorization characteristics. 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 & Costa Rica).

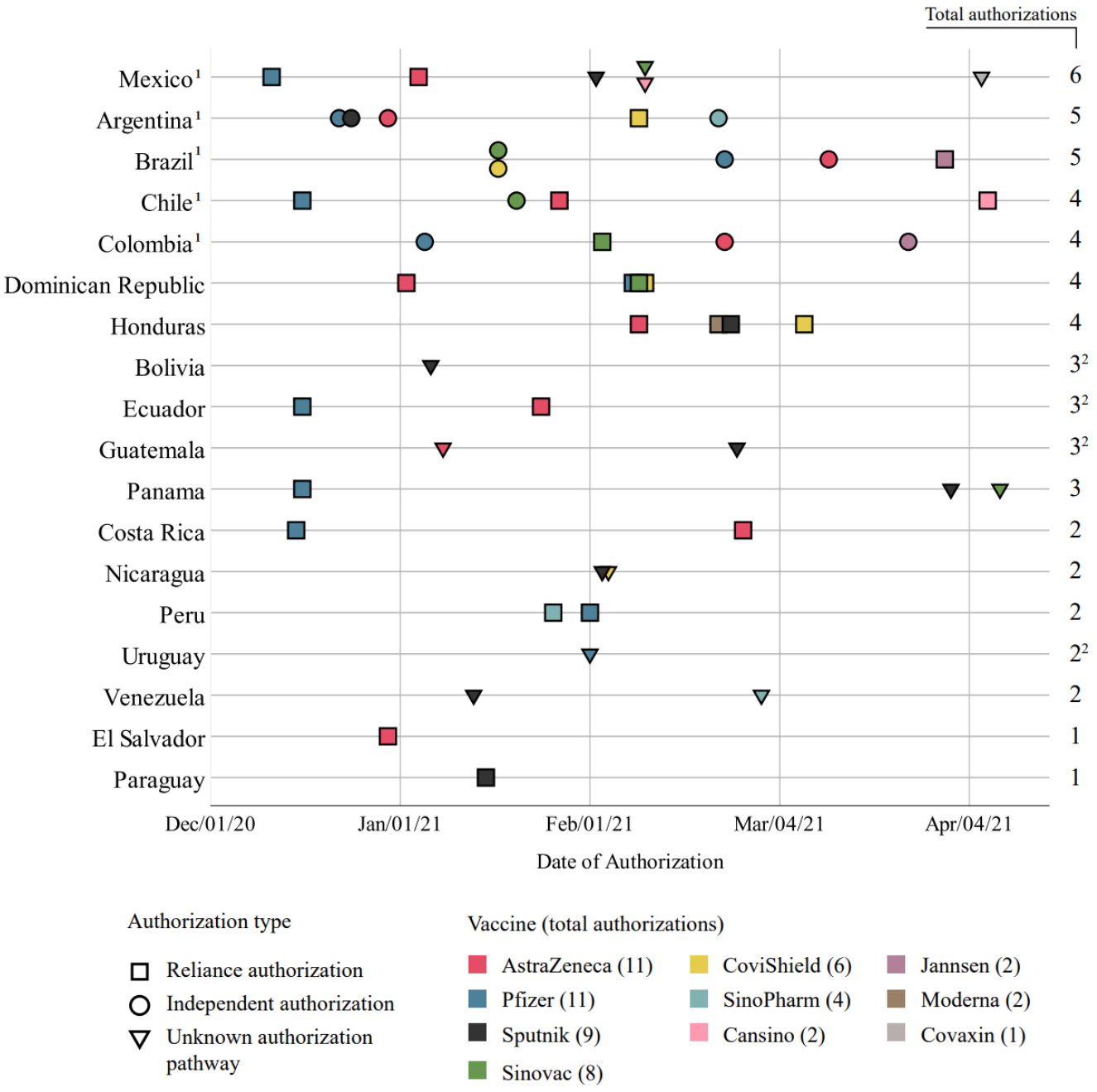

Fig 1. Timeline of COVID-19 vaccines authorizations in Latin America. Each COVID-19 vaccine authorization in Latin America with a known authorization date (n=51) is shown as a symbol on the timeline. The location of the symbol indicates the date and country of an authorization. The colour and shape of 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.

PAHO Regional Reference Authorities

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 less 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%, n=17), however, no independent authorizations by non-reference agencies were identified. Non-reference NRAs more often had unknown pathway authorizations. Table 1 provides an overview of the differences between reference and non-reference authorities.

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%)	12 (50%)	4 (16%)
Non-reference NRAs (13)	2.5 (SD .94)	32	17 (53%)	0 (0%)	15 (47%)
Total	3.1 (SD 1.41)	56	25 (45%)	12 (21%)	19 (34%)

Review times

The review time of 25 authorizations (45% of total) in 11 countries was identified (i.e., number of days between submission date and authorization date), 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 do 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).

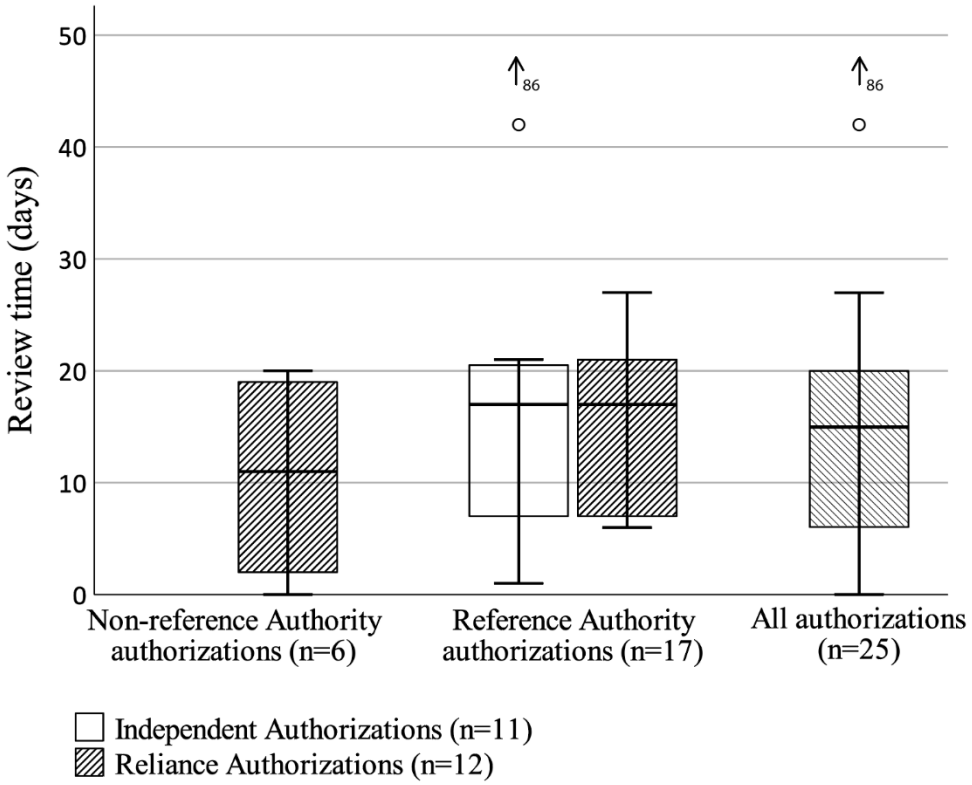

Fig 2. Clustered boxplot diagram showing COVID-19 vaccine review times of reference and non-reference authorities in Latin America by authorization type. Review time equals the number of days between submission date and the authorization date. Review times of two unknown-pathway authorizations only present under 'all authorizations'.

Discussion

Findings

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. The high prevalence (45%) 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. 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. 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 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).

Limitations

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. It was 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.

Conclusions

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, ATMPs, novel vaccines). This study demonstrated that regulatory reliance contributed to many of the rapid authorizations made by LMICs in Latin America. However, independent authorizations were expedited ass well, showing review times equal to reliance. Furthermore, reliance pathways existed before COVID-19 in several of these countries and therefore by themselves do not explain how NRAs in the region were able to effectively expedite authorizations. To nevertheless 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.

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Relianomics: Assessing the impacts of regulatory reliance

Abstract

Background: Regulatory reliance is seen as an efficient means to tackle the increasing workloads faced by National Regulatory Agencies (NRAs). However, a comprehensive understanding of the benefits and drawbacks of practicing reliance does not exist. This study lays the groundwork for "relianomics": the systematic assessment of reliance impacts.

Methods: A systemic literature search through PubMed was used to identify articles mentioning (potential) impacts of practicing reliance.

Articles mention (potential) impacts of reliance identified through PubMed and publications by global health and trade organizations were used to form a collection of 27 relevant documents. From these, the impacts of reliance and the metrics to measure them were extracted and categorized.

Results: The analyzed documents contained 24 (potential) impacts of reliance mentioned 110 times in total and 5 related metrics. Impacts were categorized into public health, economic, and internal NRA impacts. Impacts include improved NRA efficiency, enhanced NRA capabilities, unintended secondary reliance, improved access to medicine, higher quality regulatory action, risk of inheriting flawed approvals, increased collaboration, and pharmaceutical market growth. 5 of 27 documents contained empirical evidence relating to reliance.

Discussion: The Relianomics framework was informed by a comprehensive list of reported impacts and likely includes the most consequential impacts of reliance. However, empirical evidence was scarce, which emphasizes the need for a systematic approach to assessing the return-on-investment of reliance.

Introduction

Regulatory organizations are faced with increasingly complex supply chains, a globalizing pharmaceutical market, ever more sophisticated drugs, and limited human and financial resources (1). This incentivizes national regulatory authorities (NRAs) to make efficient use of available resources through collaborating with trusted NRAs from other jurisdictions by relying on each other's work and expertise, a process termed *regulatory reliance*. Regulatory reliance allows NRAs to use work performed or decisions taken by trusted NRAs in other countries to inform their own decisions and assessments. Regulatory reliance has seen a sharp rise in interest over the past decade and is generally regarded as a smart and efficient way of regulating medical products (1). Consequently, international public health institutions including the World Health Organization (WHO), Pan-American Health Organization (PAHO), Asia-Pacific Economic Cooperation (APEC), The International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), and the International Coalition of Medicines Regulatory Authorities (ICMRA) encourage NRAs to implement reliance pathways for dossier assessments with considerable attention given to how to best implement reliance pathways into the work stream of NRAs. While these guidelines provide important approaches regarding how to implement reliance, these activities are based on the assumption that reliance always has positive net effects.

WHO encourages NRAs that use reliance pathways to 'specifically measure' the impacts of reliance by establishing metrics related to regulatory decision-making such as review times, the number of products reaching the market, costs saved, and redirection of resources to areas of higher regulatory risk (2). This idea of monitoring the effects and returns of reliance is sound, but in practice quantitative analyses into the return-on-investment (ROI) of implementing reliance pathways are rare or even non-existent.

Furthermore, a comprehensive understanding of the broader impacts that practicing reliance may have outside of the regulatory process does not exist. Since the impacts of practicing reliance are not fully understood and therefore remain largely unquantifiable, decision-makers are limited in their ability to determine whether it is wise to implement or continue practicing reliance. To address this, we herein propose an approach we term "relianomics"; The systematic assessment of the societal, economic, and regulatory efficiency impacts of regulatory reliance pathways. The aim of is study is to establish the key elements underlying relianomics through a systematic review and inductive analysis of public documents that describe empirically established and theoretically suggested impacts of reliance.

Methods

Search strategy

A systematic literature search was performed to establish a body of recent articles that discussed impacts of reliance through PubMed using the following search string: (regulatory reliance) OR ("regulatory systems strengthening"). “Regulatory systems strengthening” was included as a search term since reliance is seen as an important tool within strengthening regulatory systems. Results published before 2011 were excluded to ensure the included articles are recent. Subsequently, results unrelated to regulatory science or regulatory affairs were excluded through title and abstract screening. From the remaining results, all articles mentioning one or more (in)direct impacts of reliance that are, or could potentially be, generated due to its NRA practicing reliance were included. Beside the PubMed search, publications previously known to the author(s) by organizations working in global health (e.g., WHO) and trade organizations regarding reliance were also included.

Data extraction

All included documents were searched for mentions of the known, likely, or theoretical impacts of practicing reliance. Impacts were defined as any effect of practicing reliance on any parameter and ranged from hypothesized effects to empirically demonstrated effects. Each impact was assigned a label pertaining to that specific impact (e.g., “reduces duplication of effort”). Impacts were not coded more than once per document, as analyses did not require the exact number of mentions of each impact within a single document.

Analysis

The number of unique articles in which each impact appeared was determined to assess the frequency with which the impacts of reliance were mentioned. Impacts were categorized into domains that best fit the extracted impacts, no pre-existing categories or list of impacts was used. Additionally, where relevant, impacts were nested under other broader impacts, since in some cases multiple impacts contribute to the same broader impact (e.g., expedited reviews and reduced drug prices both contribute to improved access to healthcare). Additionally, for each document it was determined whether it presented empirical evidence relating to impacts of reliance and if so, the metrics used were extracted and tied to the relevant impact label.

Results

The PubMed search resulted in 574 hits of which 392 were published in the last decade. Of these, 55 were determined to be related to regulatory science through title and abstract screening. 21 of these 55 mentioned one or more (in)direct impacts of reliance that are, or could potentially be, generated due to its NRA practicing reliance. In addition, 6 publications were identified from the author's existing library that discuss impacts of reliance from WHO, PAHO, IFPMA, the European Federation of Pharmaceutical Industries and Associations (EFPIA), and the Centre for Innovation in Regulatory Science (CIRS). Figure 1 provides an overview of the document inclusion process. (1–27)

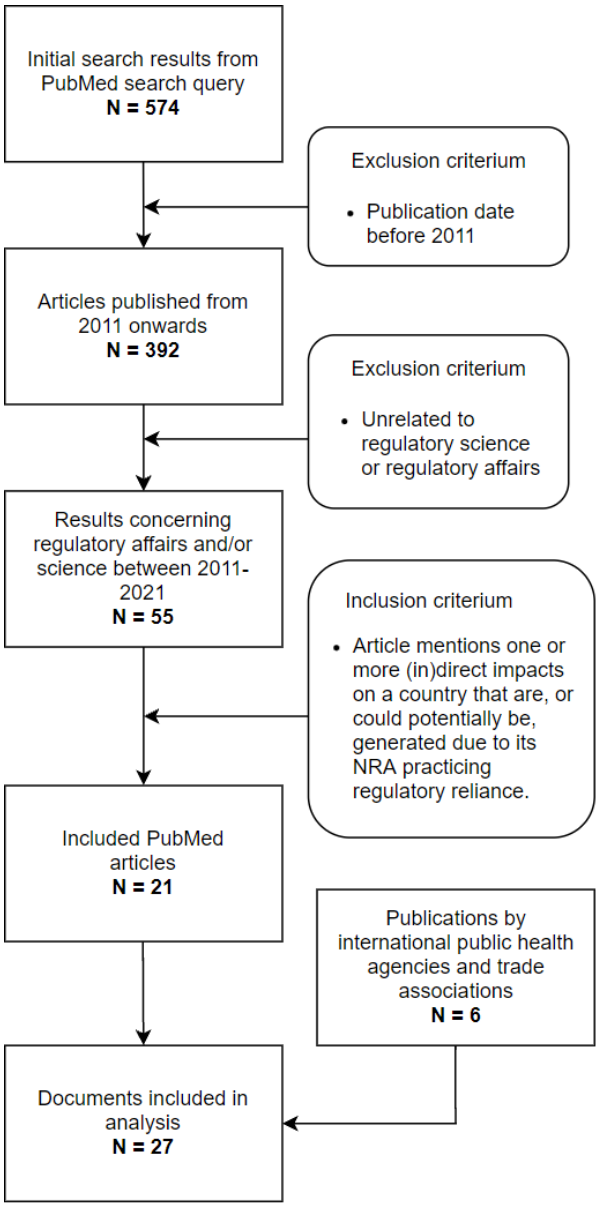

Figure 2: Literature search and exclusion process flowchart.

Analysis of the 27 included documents resulted in 24 unique impacts related to reliance mentioned 110 times in total and 5 related metrics (Table 1). Of these, 22 can be considered positives, and 2 negatives. Impacts were categorized into 3 domains: Internal NRA process impacts, public health impacts, and economic impacts. Internal NRA process impacts included all impacts that practicing reliance has on the internal affairs and capabilities of NRAs. Public health impacts cover all impacts reliance has on the quality of- and access to healthcare in a country whose NRA practices reliance. Economic impacts encompass the broader direct and indirect effects that practicing reliance may have on a country's economy. Table 1 provides details of the impacts and their domain and subcategory classifications.

Impacts on internal NRA processes

Based on the publications reviewed, reliance has a multitude of impacts on processes that take place within NRAs. In the studied documents these impacts focus on improvements in efficiency and enhancing NRA capabilities, efficiency improvements are mentioned most frequently. For example, relying on reference NRAs for dossier assessments or site inspections theoretically reduces the amount of unnecessarily duplicated work and lightens the workload for the relying NRA, allowing it to accomplish more activities with a similar amount of resources (5). Besides reducing workloads, practicing reliance is also presented as a means to enhance NRA capabilities by both strengthening in-house capabilities through learning by collaboration and by work-sharing (3), as well as being a means to address gaps in technical skills by providing access to external expertise (15).

While 17 documents only mention these efficiency and capabilities gains, some authors also address the potential downsides of reliance. Importantly, they cite the potential limitations of chains of 'secondary-reliance', in which NRAs rely on reference NRAs that, in turn, relied on another reference NRA and so on and so forth. Since it is often difficult to determine what products were approved through reliance and which were not, these chains of secondary reliance could reduce transparency of approval pathways and could also unintentionally lead to NRAs effectively relying on reference NRAs that they do not formally trust through an intermediary trusted NRA (23).

Impacts on public health

While the direct impacts of reliance are largely focused within NRAs, impacts regarding potential improvements to public health are mentioned most often in the analyzed documents. More specifically, better access to medicines and higher quality regulatory action are seen as benefits of reliance. According to the documents we reviewed, reliance impacts the access to safe, effective, and affordable medicines in three ways: shortened review timelines, lower costs, and better ability to deal with emergencies. Shortened review timeliness grant patients access to both innovative and generic medicines faster (10). Drug costs could be lowered due to increased competition in the healthcare market of a country owing to more compounds within a class being approved by its NRA through reliance (7), potentially improving affordability and thus access to medicine. And lastly, reliance is thought to help mobilize resources or ensure timely approvals in case drug shortages or health emergencies to ensure patients maintain access to the medicines they require (2,9).

Apart from impacts to access to medicine, public health in a country may benefit from higher quality regulatory action because of reliance. The reviewed documents mention three impacts that potentially cause better regulatory action: Higher quality regulatory outcomes (1) resulting from access to external

expertise, increased focus on core national value-added activities using resources preserved through reliance (27), and better market surveillance due to information sharing with other NRAs (10).

A potential pitfall of reliance described by one author is that, while relying on external assessments could bring a myriad of advantages, it comes with the risk of inheriting flawed regulatory decisions from reference agencies when implemented poorly. This could lead to NRAs approving ineffective treatments based on a reference agency while lacking the capacity to properly monitor and potentially retract said approval in light of new evidence, novel oncology drugs especially are likely to be sensitive to this issue (22,23).

Impacts on economy

Economic impacts of reliance are the least mentioned effects and are centered around market growth and collaboration. Practicing regulatory reliance could strengthen the pharmaceutical market through attracting industry to operate in a country by shortening review timelines (5,7,10). A broader impact of reliance on the economy is reliance as a catalyst for further collaboration through building trust between NRAs and in extend, counties, thus supporting increased regional, continental, and international initiatives (18).

Table 1. Categorized overview of impacts of reliance and metrics described in included documents.

Impact code	Number of documents mentioning impact*	Metrics**
Internal NRA process impacts		
Improved NRA efficiency	**16**	Number of yearly authorizations, Change in backlog size
More efficient use of resources	13	
Reduced duplication of effort	8	
Lightens workload	6	
Enhanced NRA capabilities	**7**	
Address gaps in capacity	7	
Strengthen regulatory expertise	2	
Improved access to relevant data	1	
☒ **Unintended secondary reliance**	**1**	
Public health impacts		
Improved access to medicine	**20**	
Expedited review times.	10	Review time, Time between reference and reliance approval
Better resource mobilization in response to drug shortages & health emergencies.	2	
Reduced drug costs because of more generics on the market.	1	Price difference between innovator and generic
Higher quality regulatory action	**11**	
Allows focus on core-national activities	9	
Higher quality of regulatory outcomes	3	
Better market surveillance due to information sharing	1	
☒ **Risk of inheriting flawed approvals from reference agencies.**	2	
Economic impacts		
Increased further collaboration	**4**	
Builds trust between stakeholders	3	
Support regional, continental, and international collaborations	1	
Pharmaceutical market growth	**3**	
Creates incentive for industry to operate in countries by shortening review timelines.	2	
Strengthens position of local pharmaceutical sector.	1	

*Number of unique documents an impact is mentioned in. Numbers shown next to categories (e.g., improved access to medicine) include all documents that mention impacts nested under that category + documents only mentioning the category.

**Metrics used in analyzed documents to assess a given impact, not necessary in the context of reliance pathways.

Discussion

Our analysis resulted in a broad spectrum of ideas about the impacts of reliance, ranging from empirically tested impacts to author's hypothesis. The list that resulted from this analysis (table 1) contains more impacts than would be found in any single publication and given the wide nature of the literature search it probably contains the most consequential and important impacts of reliance. However, this is the first list of its kind and cannot be interpreted as an exhaustive list that reflects a comprehensive description of all the potential impacts of reliance. Importantly, the obvious focus of publications related to reliance pathways is on the potential or observed benefits, despite the relative paucity of empirical evidence to support these impacts. Few of the statements we observed described negative considerations when planning or using reliance pathways. Yet, barriers to reliance exist (25).

This foundational list is comprised of fragments of existing documents that, even though they discuss how to best implement reliance, they are not aimed at thoroughly understanding the various impacts of reliance. A limitation to the field of assessing the impact and return-on-investment of reliance is evidenced in that the use of empirical evidence relating to impacts of reliance was discussed in just 5 of 27 publications (4,17,19,22,27) and metrics that enable assessment of reliance pathways are scarce despite WHO recommending the impact of reliance pathways to be monitored and evaluated using such metrics (2).

This imbalance illustrates the issue we aim to emphasize, namely that it remains difficult to accurately estimate the ROI of reliance because its impacts are not comprehensively understood and often remain theoretical without validated metrics or empirical evidence to back them up or assess them. Additionally, the lack of validated metrics limits decision makers considering implementing reliance, and countries that want to evaluate the impacts of their existing reliance pathways. Furthermore, this lack of reliable metrics across countries hinders meaningful performance comparisons of different reliance pathways. These types of comparisons would be valuable since they allow for designing more efficient and effective reliance pathways, as well as measuring if pathways are performing as expected.

To address this issue, we propose the development of a relianomics framework aimed at assessing reliance pathways that are either being considered by an NRA for implementation or where an NRA desires to assess existing their reliance practices. A relianomics approach should encompass all demonstrated and potential impacts of practicing reliance and be supported by their corresponding metrics. It should include 1) a categorized overview of potential impacts of practicing reliance, 2) diagnostic questions pertaining to each impact to determine whether a certain impact occurs or likely will occur, 3) a set of validated metrics relevant to each impact that enables quantification of impacts that occur or construct monitoring plans for future implementations of reliance, and 4) guidance on

how to use findings as input for subsequent relianomics calculations. These elements could then be combined into a stepwise 'manual for analysis' aimed at providing a systematic approach to assessing the impacts of implementing or practicing reliance through this framework. An overview of what a relianomics manual might address is provided in figure 2. This would allow policy makers to not only understand what impacts reliance has, but also enable them to assess whether and how much each impact is present through providing metrics for each impact and so form the basis of estimating the (potential) ROI of implementing reliance. In addition to facilitating informed decisions on implementing reliance, such a framework also enables meaningful comparisons which are essential designing better reliance pathways and optimizing existing ones.

One might argue that designing a single framework to be applicable globally is overly ambitious and will result in an unwieldy framework. However, while the measurement of each impact should indeed be standardized as much as possible across jurisdictions to ensure reliability and enable comparisons, this does not turn the framework into an unwieldy one-size-fits-all solution. Because decision-makers can weigh each impact as they see fit for their situation, this permits the flexibility to interpret these impacts in their individualized relianomics analysis. This ensures the framework is applicable across widely varying health-systems.

We realize constructing such a framework—or merely identifying the core domains is challenging and will require considerable investments of time, resources, and stakeholder alignment. Compiling a list of impacts alone would require extensive evaluation of existing reliance pathways from the regulators, industry, and patient's perspectives. We trust that our work herein can form the starting point for these evaluations and serve as a foundation to build a more comprehensive overview of relianomics impacts. But despite the effort, we believe the investments are entirely justified by the benefits and think that a relianomics framework is a prerequisite for developing our understanding of what effective regulatory reliance looks like, and that this study provides a starting point.

Reliance framework concept structure

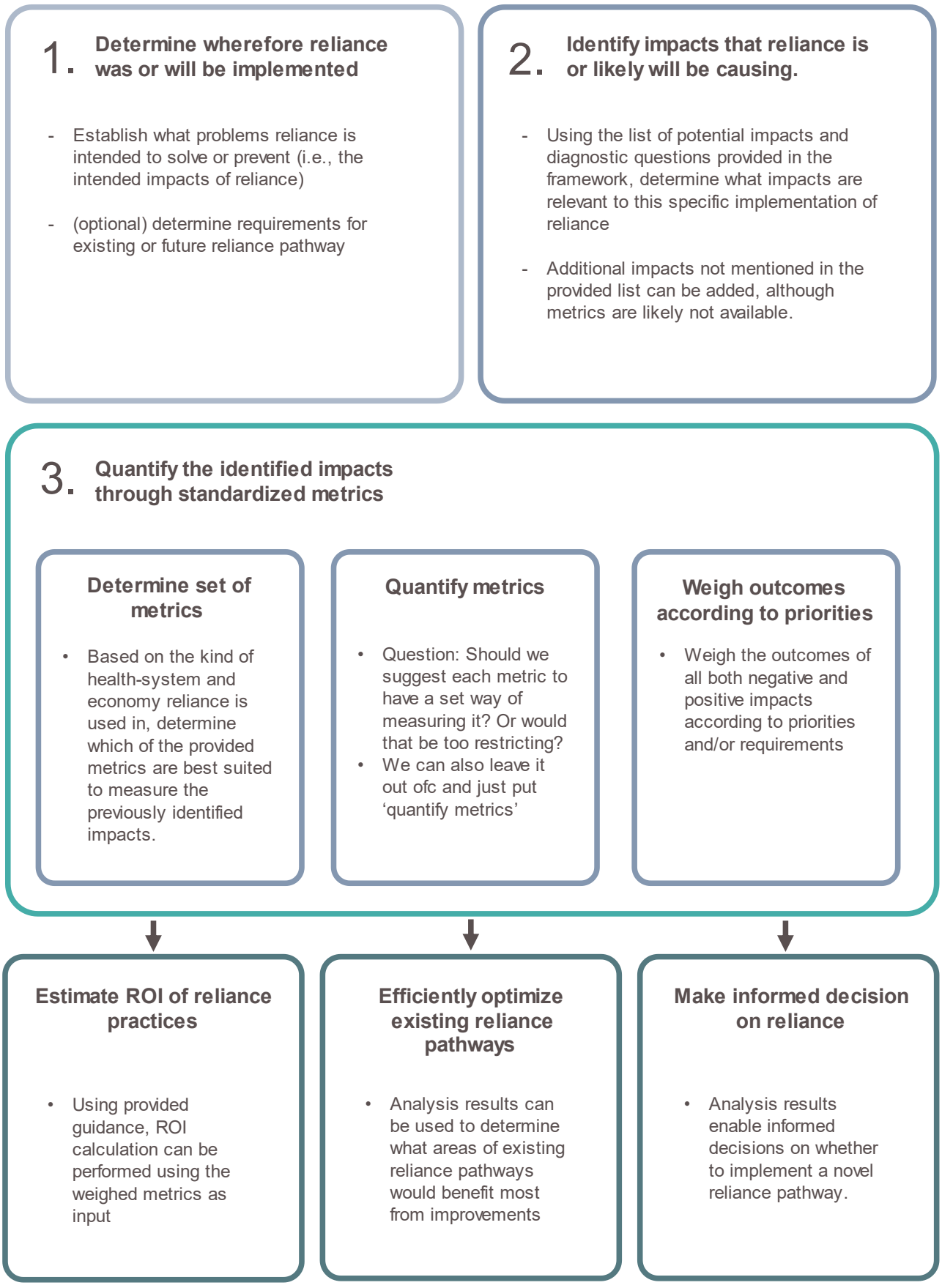

Figure 2: Overview of proposed reliance impact framework. Analysis steps are numbered 1 to 3, possible uses for results shown below.

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