Assessing the Potential Health Impact of Delays in Access to Innovative Medicines in Low- and Middle-income Countries: A Modelling Approach in Colombia

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Abstract

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Background: Access to safe, effective, and quality pharmaceuticals is unequal worldwide. Low- and middle-income countries (LMICs) face a reduced and delayed supply as well as regulatory barriers and intrinsic health system capacity limitations. The long waiting times to access innovative therapies have been previously described: however, measurement of the impact on population health outcomes has received much less attention. This study aims to explore the health impact of innovative medicine delay in Colombia, an upper-middle-income country.

Methodology: We analyzed 5 medicines for health conditions with a high burden of disease in Colombia: bevacizumab, dapagliflozin, dolutegravir, indacaterol, and ticagrelor. These medicines were recently introduced into healthcare systems and offer the potential for significant health gains. We conducted a systematic literature review for each product to establish their potential aggregate incremental health outcome gains in terms of quality-adjusted life years (QALYs) and incremental cost. The uptake and utilization of each medicine were calculated using the Colombian domestic market (SISMED Spanish acronym) and MarketScan® data set for the United States. The potential health outcomes lost were calculated as the health outcome lost due to delayed approval and uptake. Finally, a cost analysis was included for both countries.

Results: There were identified 761 cost-effectiveness analyses for the five products of interest: 47 were included in the quantitative review after applying inclusion and exclusion criteria. Most studies used QALYs as a health outcome measure (61%), were located in high-income countries (85%), and were funded by industry sponsors (82%). The delayed access in Colombia led to a potential of 34,161 QALYs lost in Colombia for the five products analyzed in a lifetime horizon, equivalent to 67% of the country's GDP.

Conclusion: LMICs face significant losses in health due to delayed access to medicines. Further research is needed to determine the causal mechanism and to strengthen the incentives for different stakeholders to pursue collaborative efforts at the global, regional, and national levels towards improving the access to medicines globally and locally.

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BACKGROUND AND SIGNIFICANCE

Access[1] to safe, effective, and quality pharmaceuticals is unequal worldwide. Low and middle-income countries (LMICs) face a reduced and delayed supply from the producer side. During the COVID-19 pandemics, the United States and Europe had access to COVID-19 vaccines at least four months before most LMICs, and many high-income countries (HIC) requested more doses than required by their population.[1,2] Furthermore, less than 1% of the doses administered globally have been allocated in low-income countries, and their population coverage is less than 2% of their populations.[3,4] Moreover, this inequitable access is exacerbated by intrinsic factors in local settings, including high out-of-pocket health expenditures, relatively inexperienced health insurance systems, and sometimes cumbersome pharmaceutical policy regulations.[5]

Global healthcare systems' ability to provide full and affordable access to health care is facing additional pressure due to the rising prices of innovative medicines. Global health spending more than doubled in real terms over the last twenty years, reaching 10% of global GDP.[6] In 2018, global pharmaceutical spending was estimated to be 1.2 trillion USD and is projected to rise above 1.5 trillion USD by 2023, representing an annual growth rate of 3-6% derived mainly from the United States and emerging pharmacologic markets as well as the adoption of new innovative products. Moreover, by 2023, 61% of the medicine spending globally will be on original brand pharmaceuticals, corresponding only to approximately 12% of volume.[7]

Innovative medicines are unique economic goods due to a combination of several factors. First, they have the potential to improve the health of patients globally.[8,9] Once the innovation reaches the market, the marginal cost of production for additional doses is often very low. Second, their development is costly and uncertain, with only 30 to 50 new products approved each year.[10] The whole process from new medicine discovery to approval for use might take over a decade and only 10% to 20% of drugs that begin human clinical trials end up being approved for marketing.[11] Limited information is available about the required investment needed to bring a new medicine to market, it might range between $314 million to $2.8 billion and an estimated mean of $1.34 billion.[12] Third, their development financing relies on intellectual property protection. Patents and international treaties, as the Trade-Related Aspects of Intellectual Property Rights (TRIPS)), aim to incentivize innovation through provision of a temporary monopoly market with the ability to establish a high initial price.

With the costs of research and development (R&D) of new medicines rising[13] and the accompanying pattern of rising prices, countries worldwide have struggled to keep up given limited resources. One way to manage this is to delay access. The European Federation of Pharmaceutical Industries and Associations (EFPIA) gathers data on delays, publishing a "Waiting to Access Innovative Therapies" (WAIT) indicator. This indicator measures the availability of new medicines in the different EU Member States, defining availability as the inclusion of approved medicine on the public reimbursement list in a country. It shows access inequities within Europe: patients in central and eastern Europe and from small

[1] Defined by the WHO as: "The reliable and consistent availability of appropriate essential, quality medicines at health facilities, the rational prescribing and dispensing of such medicines, and ensuring that they are affordable. Out-of-pocket payments, if any, should be well within patients' capacity to pay, and protection against catastrophic expenditure should be ensured"[40]

states have long waiting times to access new treatments. On average, Romanian citizens wait 2 years more than German citizens to gain access.[14]

All of this raises the question of how significant these delays might be in lower-income settings, and what are the consequences for population health. The aim of this analysis is to explore the impact of pharmaceutical access delays in Colombia, an upper-middle-income country, but one with substantial income inequality.[15]

METHODOLOGY

We chose Colombia to perform a study case to assess the impact of delayed access to innovative medicines in LMICs. We were interested in exploring two main questions: what is the nature and size of access delays, and what is the potential health loss as a result of the delay? Five disease areas were selected based on substantial "unmet medical need" but with relatively recently introduced medicines possibly offering significant health gains. To establish the extent of the delay in access, we gathered information on the approval dates for each of the medicines in the U.S., Europe, Colombia, and other LMICs. Approval in the U.S. was taken as the earliest potentially feasible date. Uptake levels in Colombia were assessed to estimate possible differences in access as compared to the US. To estimate the potential health impacts of access delays for each of the five medicines, we conducted a systematic literature review of published cost-effectiveness analyses to establish the potential effectiveness of each of the five products.

Country Selection: Colombia

Health and access to healthcare is considered a basic constitutional right in Colombia. The healthcare system provides universal health coverage (UHC) through a mix of public and private insurance plans and hospitals. There are two main health insurance plans: contributory and subsidized. The contributory insurance covers formal workers with premium payments from the employee and employer. The subsidized insurance is publicly-funded and covers the lower-income population. It is financed by the government through taxes plus a percentage of the premiums paid in the contributory plan as a redistributive measure.[16] Colombia, an upper-middle-income country, has an out-of-pocket spending share similar to the European Union (15%), which is far below the Latin American average (30%) and somewhat below the global average (18%).[17] The insured individuals choose their insurer, and care providers within the insurer's network and receive a purchase by insurers through contracts from public or private providers.[16] The benefits plan in Colombia includes primary care, outpatient care, dental care, eye care, drug coverage, hospitalization, and emergency care. In 2007, the premium equivalent of the package was US$207 annually.[16] Nonetheless, the limited out-of-pocket payments and the comprehensive health benefits package in Colombia still result in implicit rationing and inequitable distribution of access to healthcare services.[18,19] This contrasts with some other publicly-paid health systems that are more likely to use strict cost-effectiveness measures to determine which services (particularly new medicines) are covered and their reimbursement amounts. Furthermore, the main private-pay health system has lower restrictions to determine which service gets into the market, but a higher out-of-pocket expenditure.[20]

In terms of pharmaceutical policy, Colombia is an "emerging market" that imports most of the new pharmaceuticals that it receives. Colombia has an intersectoral approach aimed at achieving equitable access to effective medicines with "quality service and shared responsibility.[21] The policy focuses on

identifying and regulating the nonrational use of medicines, limiting inefficient spending, and improving the poor supply and dispensing system.[21] The benefit package has an implicit general approach to coverage with an explicit list of medicines excluded. The pharmaceutical market is regulated by the Ministry of Health (MoH) through the National Institute of Food and Medicines Surveillance (INVIMA) and the Institute of Technology Assessment in Health (IETS). The medicines regulatory environment has high registration requirements and updates its formulary every two years. The regulatory agency in Colombia is called INVIMA ([Spanish acronym]: Instituto Nacional de Vigilancia de Medicamentos y Alimentos) and it assumes the functions performed by the FDA in the United States or the EMA in Europe. It requires an assessment of efficacy, safety, bioequivalence, and bioavailability at the national level. On average, it takes 22 months to register a new medicine in Colombia and 12 months to include it on the reimbursement list, compared to the nine months in most OECD countries.[22] Furthermore, the national health technology assessment (HTA) agency (IETS – [Spanish acronym]: Instituto de Evaluación Teconologica en Salud) evaluates the potential cost-effectiveness of new medicines and reports its findings to the National Drug Price and Medical Devices commission (CNPMDM, [Spanish Acronym]: Comisión Nacional de Precios de Medicamentos y Dispositivos Médicos) to negotiate the market price.

In 2011, the Colombian government implemented a new comprehensive pharmaceutical policy, including regulations for new generic biotechnological medicines, drug price regulation, increased price transparency, and HTA. At the beginning, the CNPMDM regulated the prices using the median wholesale price less a fixed percentage (20%) as a cap. Subsequently, in 2013, the regulation transitioned to an external price referencing (EPR) system for selected therapeutical groups that are considered of public interest and they do not have a therapeutic substitute or it has a high market concentration.[23] The EPR regulation identifies medications with higher demand, higher prices, and higher financial impact each year. Then, the regulator selects the medicines within highly concentrated markets, and it uses the external reference pricing as a price control for both on-patent and off-patent medicines. After the price cap regulation implemented between 2011 and 2014, Colombia saw an average price decrease of 43% on nearly 1000 medications. However, this was offset by a 26% increase in utilization of medications and an increased the public and private pharmaceutical health expenditure.[23,24]

Product selection

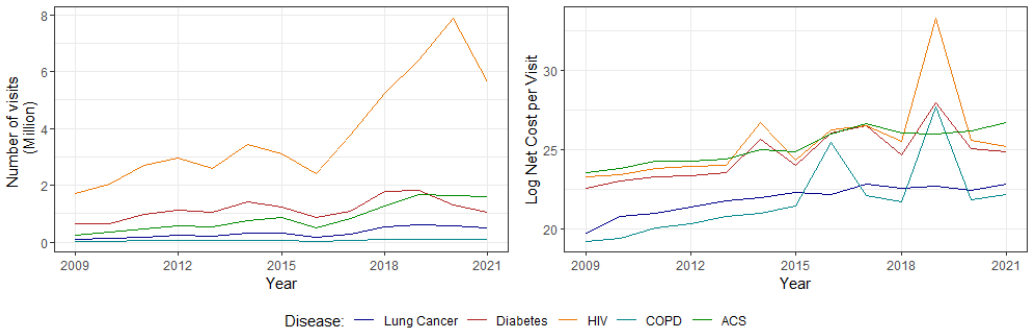

Figure 1. Health Services Utilization and Cost in Colombia by Condition. Figure created by the author using RIPS data set ([Spanish acronym]: Registros Individuales de Prestación de Servicios= from 2009 - 2021.[25] HIV: Human Immunodeficiency Virus, COPD: Chronic Obstructive Pulmonary Disease, ACS: Acute Coronary Syndrome.

Five medicines were selected based on the burden of disease in Colombia, according to the mortality rates and estimates of the impact in term of disability-adjusted life-year (DALYs) lost.[26,27] These included: lung cancer, diabetes type II, HIV, chronic obstructive pulmonary disease (COPD), and acute coronary syndrome. Figure 1 shows the number of visits and cost per visit for the period 2009 to 2021 for each of the five disease conditions. For each condition, the international clinical treatment guideline was reviewed and identified medicines approved in the last 15 years. We selected five medicines for detailed impact analysis: bevacizumab, dapagliflozin, dolutegravir, indacaterol, and ticagrelor. Each of these medications can be prescribed in conjunction with other medicines. These five products also belong to the leading therapy areas for spending in the United States by 2018.[7]

Literature review

Search

From the literature of cost-effectiveness analyses (CEAs) for each of the five products, we developed a data set of the estimates of incremental quality-adjusted life-year (iQALY) gains, increment life-year (iLY) gains, incremental disability-adjusted life-year (iDALY) losses, and incremental costs associated with these medicines. We used a similar methodology as Chambers et al (2017).[28] For each product, we conducted a systematic review of the literature using PubMed and Google Scholar for CEA studies published any time before February 8, 2022. We followed the PRISMA guidelines in searching for original peer-reviewed articles published in English or Spanish worldwide. There were no restrictions on the publication year. To identify relevant articles, we used the following terms combined with MeSH terms: “Cost-effectiveness”, “CEA”, “QALY”, “DALY”, “life year, “life-year gained”, “ICER”, “bevacizumab”, “dapagliflozin”, “dolutegravir”, “indacaterol”, ‘ticagrelor”, “Avastin”, “Farxiga”, “Forxiga”, “Arcapta Neohaler”, “Ultibro Breezhaler”, “Brilinta”. Moreover, we expanded the search using citations in the reference lists of the articles.

Studies were screened using titles and abstracts and then the full text was reviewed for the selected articles. The article had to be original research in English or Spanish for the health condition of interest. To be included in the analysis, the article should also report the incremental cost-effectiveness ratio (ICER), incremental outcome (iQALY, iLY, or iDALY), incremental costs, time horizon, discount rate, and economic perspective. We also extracted data related to publication and study design, including funding source, final cost-effectiveness conclusion according to the threshold used, robustness checks, study location, health condition, intervention, comparator, health outcome, perspective, year of cost, and publication year, and base-case results. The ICER and the incremental costs were extracted when they were available or calculated based on the incremental outcome and the available second measure (ICER or incremental cost). We collected the costs and ICERs in the currency reported by the study and translated them into US dollars for the same year. For comparison across studies, we converted the costs and ICERs to 2021 US dollars, adjusting for inflation and exchange rates. When a study compared the drug of interest with multiple alternatives, analyzed multiple countries, or uses different time horizons, we added each of them to our dataset. We excluded studies that took a non-payer perspective, and studies that compared the drug of interest to a placebo comparator since all health conditions included have active treatment.

Analysis

We created a dataset with the studies that met both the inclusion and exclusion criteria. We performed an exploratory analysis of the relationship between the publication variables and the study results. We used nonparametric statistical tests to compare the proportion distribution of the funding source with the study location by country's income. We used Kruskal-Wallis test with a 0.05 level of significance. Additionally, selected subsamples of the studies using the comparability criteria for the case study. We included studies with a "lifetime horizon" defined as follows: (a) at least four years in advanced non-small lung cancer, (b) at least 20 years in diabetes, and (c) at least 10 years in the other indications. The remaining selection criteria are described in Table 1. If a study used several horizon times, we chose the longest to be included. Using these subsamples, we estimated incremental health outcomes and incremental costs. We also calculated median values to avoid a high influence of outlier values.

Table 1. Study Population Definition for Each Condition

Product	Brand Name	Comparability criteria
Bevacizumab	Avastin	Advanced NSCLC; first-line intervention; no maintenance intervention; no EGRF mutation subpopulation
Dapagliflozin	Farxiga	T2DM not controlled with metformin; intervention not used as monotherapy or added to insulin, excluding similar level indications (e.g,. same family drug or DPPi4)
Dolutegravir	Tivicay	HIV-naïve patient; discount rate different than zero
Indacaterol	Arcapta Neohaler	Moderate to severe COPD; ICER different from zero
Ticagrelor	Brilinta	ACS, excluding subpopulation with PCI indication; comparator should include ASA as the guidelines indicates DAPT; discount rate different than zero

NSCLC: Non-small cell lung cancer, T2DM: Type 2 Diabetes Mellitus, HIV: Human Immunodeficiency virus, COPD: Chronic Obstructive Pulmonary Disease, ACS: Acute coronary syndrome, ASA: aspirin, DAPT: Dual Antiplatelet Therapy

Case Study: Uptake and Utilization of five medicines in Colombia

Data sources

We used the official database for prices and quantities sold in the Colombian domestic market (SISMED [Spanish acronym]: Sistema de Información de Precios de Medicamentos) and MarketScan® Commercial Claims and Encounter health insurance dataset from 2007 to 2020. SISMED data contains monthly data on purchased price, sales price, sold units, type of market (private and institutional), and type of seller (laboratory, wholesalers, health providers, and insurers). It covers the period from 2012 to 2020. The MarketScan database captures individual clinical utilization, expenditures, and prescription drug services longitudinal de-identified patient-level data. It contains data from commercial insurers and Medicaid insurance. It is representative of the US population. We filtered drug claims using the NCD number for the five products. We used the patients' outpatient and inpatient services claims to filter the claims for the target health condition using the diagnosis codes described in Table A1 in the Appendix. We included only enrollees aged 18 years or older and two claims with a corresponding diagnosis code for the target health conditions. We used the diagnosis codes from the International Classification of Disease, Ninth and Tenth revision (ICD9 and ICD 10 respectively).

Analysis

The health outcome lost analysis only included QALYs since the DALYs data were only available for dolutegravir in two studies. The potential QALYs lost were calculated as the QALYs lost due to delayed approval. The first component compared the impact of delayed approval date in Colombia versus the earlier approval in the United States or Europe depending on which on occurs first. We used the Colombian uptake and utilization slopes to model what would have happened if the Colombian approval dates were the same as the one in the chosen HICs comparator. The dates of approvals are shown on Table A2 in the Appendix. Three scenarios were modeled to address the usual incremental uptake and utilization slopes. The (i) "worst case" assumes that only 10% of the individuals who potentially benefit from the medicines have access to it before the actual approval date. The actual utilization slope in Colombia was used as the potential utilization during delayed access period, using (ii) the first year of available data and (iii) the current utilization. The data from Colombia were transformed from sold units to utilization per individual using the number of units by the dosage per product per year. The potential preventable QALYs lost were then calculated using the formula (1).

1) $Aggregate\ QALYs\ Lost\ due\ to\ Dealyed\ Approval = ((Utilization\ per\ year * iQALYs)/12months) * months\ delayed\ approval$

Given this total estimate, the impact is also expressed in monetary terms using the Colombia GDP per capita as the estimate the societal willingness to pay (i.e., the cost-effectiveness threshold). An additional analysis of commercial prices of medicines in both countries was performed. The results of this analysis are included in the Appendix and are discussed briefly below. The data were analyzed from March to June 2022, using SAS software version 9.4 (Copyright© SAS Institute Inc) and R, version 4.2.0 (R Foundation for Statistical Computing) software.

RESULTS

Literature review

The search identified 761 CEAs for the five products of interest. We removed 182 duplicate studies, and 445 after screening by title and abstract. A total of 88 studies satisfied the inclusion and exclusion criteria. We included 47 studies in this analysis based on comparability criteria. Figure A1 in Appendix shows the flow chart based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

A total of 285 observations on the outcomes of interest were obtained from the 47 studies selected. Table 2 summarizes some key characteristics and outcomes reported in the studies by target product. Most studies were implemented in high-income countries (HIC) (85%) and sponsored by the industry (82%). QALYs were the health outcomes most frequently used (61%) followed by the LYG (38%). Only 3 studies used DALYs, and each of them evaluated Dolutegravir, an HIV drug. Most studies used a 3% discount rate and a lifetime horizon. The assessed intervention was reported to be "cost-effective" in 94% of the studies, and it was reported "dominant" 38% of the time. Most industry-funded studies were located in HICs (Kruskal-Wallis test: $p < 0.001$ in both cases). Table 3 shows the aggregate values calculated for the study case.

Table 2. Case Study Literature Review Summary

Variable	Overall, N = 122[1]	Bevacizumab, N = 12[1]	Dapagliflozin, N = 16[1]	Dolutegravir, N = 37[1]	Indacaterol, N = 25[1]	Ticagrelor, N = 32[1]
Health Outcome						
DALY	2 (1.6%)	0 (0%)	0 (0%)	2 (5.4%)	0 (0%)	0 (0%)
LYG	46 (38%)	7 (58%)	6 (38%)	10 (27%)	12 (48%)	11 (34%)
QALY	74 (61%)	5 (42%)	10 (62%)	25 (68%)	13 (52%)	21 (66%)
Location						
High income	104 (85%)	9 (75%)	14 (88%)	33 (89%)	21 (84%)	27 (84%)
Upper middle income	10 (8.2%)	3 (25%)	0 (0%)	0 (0%)	4 (16%)	3 (9.4%)
Lower middle and Low income	8 (6.6%)	0 (0%)	2 (12%)	4 (11%)	0 (0%)	2 (6.2%)
Funding						
Unfunded	7 (6.4%)	2 (18%)	0 (0%)	0 (0%)	5 (20%)	0 (0%)
Non-industry related	13 (12%)	5 (45%)	2 (13%)	4 (12%)	0 (0%)	2 (7.7%)
Industry	90 (82%)	4 (36%)	13 (87%)	29 (88%)	20 (80%)	24 (92%)
Discount Rate						
2.5	2 (1.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (6.2%)
3	86 (72%)	7 (64%)	10 (67%)	23 (62%)	25 (100%)	21 (66%)
3.5	7 (5.8%)	3 (27%)	3 (20%)	0 (0%)	0 (0%)	1 (3.1%)
4	2 (1.7%)	0 (0%)	2 (13%)	0 (0%)	0 (0%)	0 (0%)
5	22 (18%)	1 (9.1%)	0 (0%)	14 (38%)	0 (0%)	7 (22%)
6	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3.1%)
Lifetime Horizon	122 (100%)	12 (100%)	16 (100%)	37 (100%)	25 (100%)	32 (100%)
Dominant Intervention	46 (38%)	0 (0%)	0 (0%)	30 (81%)	16 (64%)	0 (0%)
Cost-Effective Intervention	115 (94%)	6 (50%)	16 (100%)	36 (97%)	25 (100%)	32 (100%)

[1] n (%)

Table 3. Median and Range of Incremental Values by Product

Variable	**Bevacizumab**, N = 10[1]	**Dapagliflozin**, N = 10[1]	**Dolutegravir**, N = 27[1]	**Indacaterol**, N = 13[1]	**Ticagrelor**, N = 23[1]
iQALY	0.33 (0.13, 0.34)	0.34 (0.26, 0.46)	0.12 (0.10, 0.17)	0.20 (0.14, 0.24)	0.13 (0.11, 0.14)
iLYG	0.50 (0.17, 0.86)	0.08 (0.07, 0.10)	0.33 (0.24, 0.41)	0.30 (0.19, 0.31)	0.15 (0.14, 0.16)
iCost (US$)	47,542 (23,549, 90,037)	2,512 (1,943, 2,714)	-12,863 (-27,458, -1,281)	-2,121 (-5,641, -290)	984 (686, 1,306)

[1] Median (IQR)

DALYS data not present since there are only two observations for Dolutegravir

Table 4. Aggregate Health Impact by Product

Medicine	Aggregate QALYs Lost			Monetary valuation (US$)
	Delayed Approval			
	Worst Case (10% prevalence)	Utilization in First Year	Utilization Peak	
Bevacizumab	261	997	4595	24,502,331
Dapagliflozin	93888	3191	21524	114,768,102
Dolutegravir	2340	276	1047	5,583,559
Indacaterol	7298	643	1988	10,598,922
Ticagrelor	1159	967	5007	26,694,973
Total	**104946**	**6076**	**34161**	**182,147,887**

Study case

The approval dates in Colombia were shorter than expected based on the literature and industry reports. The uptake in the US has a steeper slope compared to the Colombian uptake and the US has already reached the peak, while the Colombian utilization continues increasing until 2019. In 2019, the trends in both countries have a further decrease for most medicines probably explained by the COVID-19 pandemic's impact on the provision of other health care services (Figure A2 in Appendix). Further, most utilization slopes in Colombia are steeper after 2019, which coincides with the inclusion of these medicines in the official formulary to be paid through capitated payments. Finally, the utilization slopes of bevacizumab and indacaterol in the US are interesting since it is decreasing, and it might be explained by use of substitute medicines. Currently, the indacaterol is no longer commercialized in the US market, but it Is commercialized in Colombia, and Europe among others.

In general, the price in the US follows a concave curve with a low price at the market introduction followed by increases until a peak and finally decreases over a period of 6 to 10 years. In contrast, the prices in Colombia have a decreasing slope for three medicines (indacaterol, ticagrelor and dolutegravir) and an increasing slope for the two remaining drugs (bevacizumab and dapagliflozin). A comparison of the introductory prices (or the first price available) is presented in Table A3 in the appendix.

The aggregate health impact due to delayed approval by product is shown in Table 4. The QALYs lost calculated using the utilization data in Colombia are lower than the worst-case scenario in all the medicines except bevacizumab, meaning that less than 10% of the population who need the medicine

accessed to it after the approval. Dapagliflozin has the largest QALYs lost probably due to the high prevalence of diabetes mellitus type two in Colombia.

DISCUSSION

The delayed access led to a potential 34,161 QALYs lost using the utilization in the peak year in Colombia for the five products analyzed. The total monetary valuation of these lost QALYs is USD182 million, which represents 67% of Colombian GDP and it is higher than the Colombian annual health expenditure in a lifetime horizon.[29] Likewise, the literature review shows variability in the effectiveness calculated in each study even when the model parameters such as discount rate and life horizon are the same. This might be explained by the intrinsic variability in each health system to implement the use of a medicine once it is approved and introduced in the local market. Moreover, the incremental gain in health outcomes depends on the current best alternative treatment available within the country. For instance, the utilization curves show, not surprisingly, that while Colombia is still increasing the utilization of all the studied medicines, in the United States the utilization has already reached its peak and it is declining probably by the substitution with a new product.

Based on this study, it is not possible to establish a causal mechanism for these findings since there are many factors affecting the delayed uptake and underutilization. For instance, the COVID-19 pandemic negatively affected medicine use and spending globally. And there was a decrease in chronic disease treatment such as hypertension and diabetes.[30] Nonetheless, there are long-term factors that influence the access to medicines in Colombia and other LMICs, including regulatory, pricing, and local health system barriers. While some countries have adopted the FDA or EMA approval as their approval standard, others have developed their own regulatory agencies to test locally the safety and effectiveness of the medicines, which takes time and heavy research efforts. Prices influence the demand for new pharmaceuticals due to the impact on local budgets. Finally, the local health system's capacity to adopt and distribute a new medicine also plays a role in the uptake and utilization of medicines. Due to the multifactorial reasons behind the unequitable access to medicines worldwide, the health policies aimed to reduce this gap should be a conjunction of efforts at the global regional and local levels among governments, industry, and non-profit organizations.

Reducing the regulatory burden on LMICs might speed up the approval date and uptake of new medicines. This can be reached by expanding prequalified medicines by WHO and strengthening the regional harmonization strategies. The WHO prequalification of medicines process includes a comprehensive evaluation of quality, safety and efficacy of the product. WHO certifies that the manufacturing sites comply with manufacturing practices.[31] This WHO prequalification list includes 625 medicines targeted priority disease such as malaria, tuberculosis, HIV, and hepatitis. Furthermore, the regulatory harmonization is a collaborative effort to increase the limited national capacity to regulate medicines. For instance, the East African Community regulatory harmonization initiative join the capacities of six national regulatory authorities to improve the legal frameworks and governance of the registration, inspection and quality management system in the region, improving the access and reducing substandard and falsified medicine distribution.[32]

Increasing manufacturing and developing capacity at local and regional level might decrease the price and increase access to medicines. The COVID-19 pandemics highlighted the “national security” concerns that about most research and development (R&D) companies are located in high-income countries and less than 1% headquartered in Latin America or Africa. The United States houses 44% of the R&D

companies and 53% of current medicines research, while China has 12% of the companies and 21% of the ongoing research.[33] This high concentration is closely related to an unequal distribution of the final product, which raises the necessity to strengthen the local drug production and distribution in the Global South[4] For instance, researchers in South Africa are replicating Moderna's COVID-19 vaccine based on the public data of DNA molecule information with the hope of getting a patent license once the vaccine is ready.[34] Likewise, some vaccine makers have announced manufacturing partnerships and built manufacturing sites in LMICs such as Argentina, Rwanda, and South Africa.[4]

Economists[35] have long argued for differential pricing across countries based on ability to pay. This approach would not only be more equitable but also more efficient in terms of generating a higher rate of innovation. Nonetheless, there are substantial operational barriers to making this happen in part because it requires HICs to accept the fact that others would pay less, and through "external reference pricing" (ERP), they often try to tie their prices to prices in lower-income countries.[36] Prices for innovative medicines do vary across countries, but their correlation with the ability to pay is often low. There are some notable exceptions, mainly in the treatment of infectious diseases such as HIV medicines, vaccines, and direct-acting antivirals for HCV. Although efforts to increase this treatment access globally have saved thousands of lives, focusing on infectious diseases have left other disease with neglected treatment access.[37,38]

This study has some limitations. The dataset for Colombia was available only from 2012, so the initial uptake for three products was not observed, and United States claims database began in 2007, and it did not include the uptake of bevacizumab immediately after its introduction. Furthermore, process for data-gathering in the datasets differs and aims to measure different variables. The Colombian datasets include all the country's pharmaceutical trades by units, but there is no individual patient information that allows filtering it by indication. The MarketScan® data set is a sample of individuals with commercial insurance, and it does not represent a comprehensive source of the total unit trade in the United States.

Improving the equitable and timely access to safe, efficient, and quality medicines in LMICs should be a priority the global pharmaceutical policy.[39] It requires collaboration among different stakeholders and national and international levels. There is no a unique ideal policy alternative. Every potential policy should be analyzed carefully to weigh the trade-offs, balancing the best from each alternative with possible unintended negative impacts. For instance, the price control policies aim to improve affordability but might negatively impact the medicines' availability due to pharmaceutical companies' production cut-offs.[33] Likewise, advocating for increased price transparency might increase the accountability and reduce information asymmetries in the market, but might disincentivize the differential pricing policy. Further research is needed to better understand the incentives for each stakeholder to pursue efforts towards reducing the inequitable access to medicines globally. This research supports these efforts by estimating some of the negative consequences of current global practices.

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APPENDIX

Table A1. Diagnosis code used on MarketScan® claims analysis

Product	Indication	ICD-10	ICD-9
Bevacizumab	NSCLC	C340, C341, C342, C343, C349	1622, 1623, 1624, 1625, 1628, 1629
Dapagliflozin	T2DM	E11X	25000, 25002, 25010,25012, 25020, 25022, 205030,20532, 25040, 25042, 25050, 25052, 25060, 25062, 25070,25072, 25080, 25082, 25090,25092
Dolutegravir	HIV	B20X, B21X, B22X, B23X, B24X	042
Indacaterol	COPD	J440, J441, J449	49120, 49121, 49122
Ticagrelor	ACS	I249, I248, I21X, I22X	410, 4118

NSCLC: Non-small cell lung cancer, T2DM: Type 2 Diabetes Mellitus, HIV: Human Immunodeficiency virus, COPD: Chronic Obstructive Pulmonary Disease, ACS: Acute coronary syndrome, ICD: International Classification of Disease.

Table A2. Time in months since approval in Colombia

Location	Medicine				
	Bevacizumab	Dapagliflozin	Dolutegravir	Indacaterol	Ticagrelor
US - First approval[1]	-33	-13	-13	10	-5
US - Target indication	-1	-13	-13	10	-5
Colombia (Equals zero)[2]	11/10/2006	2/9/2015	8/22/2014	9/7/2010	12/21/2011
EMA[3]	11	-27	-7	-9	-13
Mexico[4]	161	-23	2	62	35
Chile[5]	-18	42	-9	-7	-3
Costa Rica[6]	86	54	62	123	70

Table A3. Price of month doses at introduction year by product and country

Medicine	Colombia		US	
	Year	Price ($US)	Year	Price ($US)
Bevacizumab	2012	191.27	2007	20,640.50
Dapagliflozin	2015	24.40	2014	853.88
Dolutegravir	2015	235.59	2013	2669.94
Indacaterol	2012	54.12	2012	345.19
Ticagrelor	2012	127.51	2011	307.38

Figure A1. PRISMA flow diagrams of screened articles

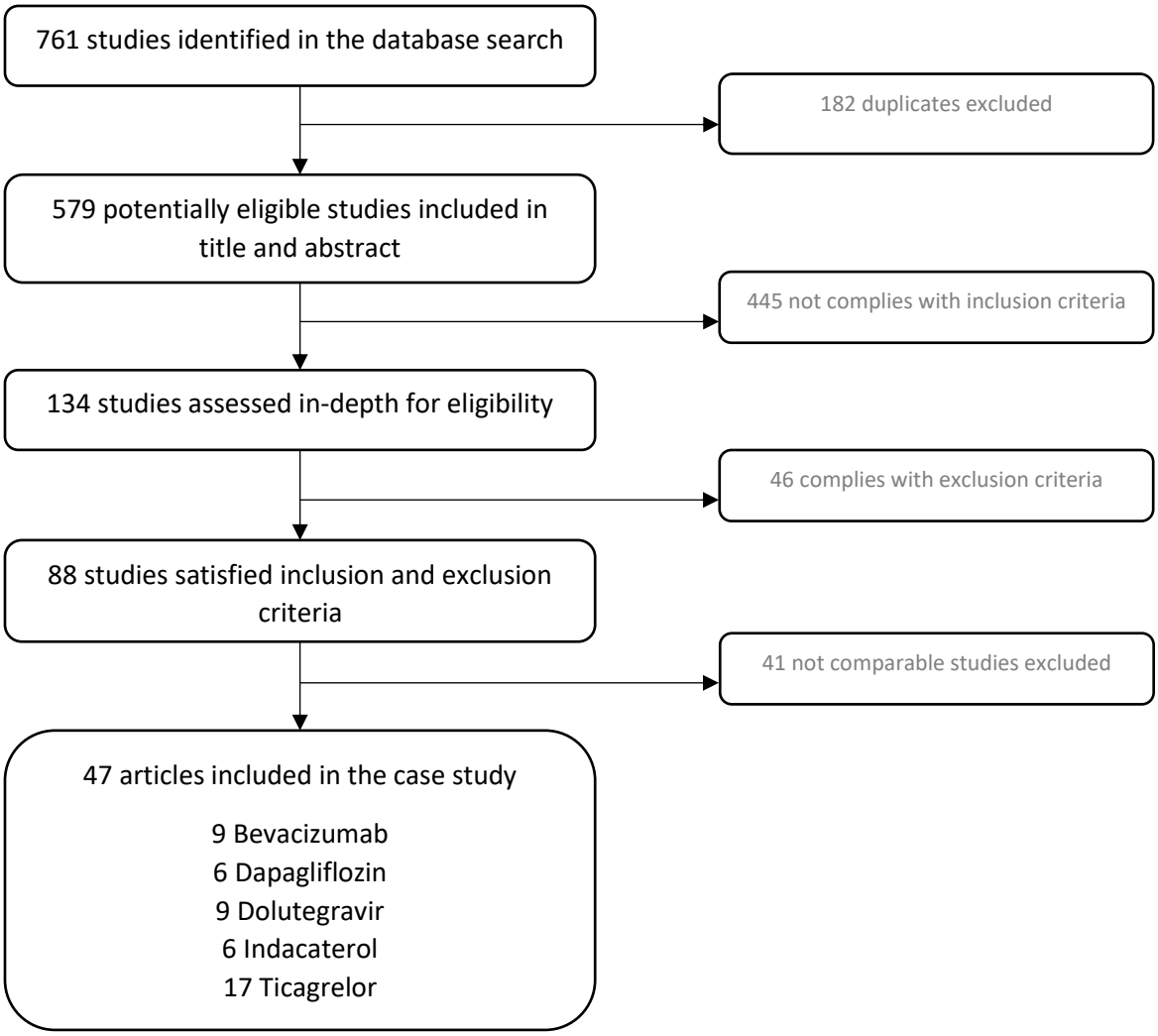
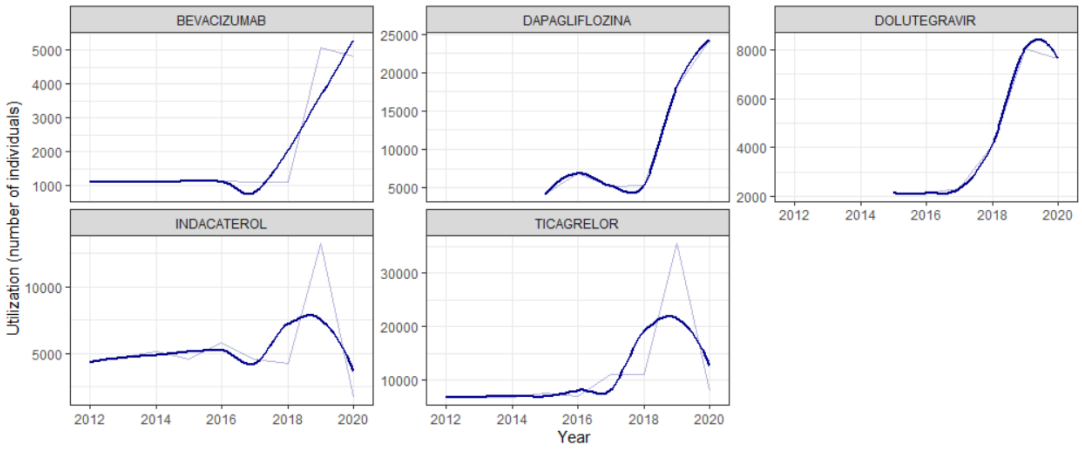


Figure A2. Uptake and Utilization Slopes by Product

a. Colombian slopes



b. US slopes

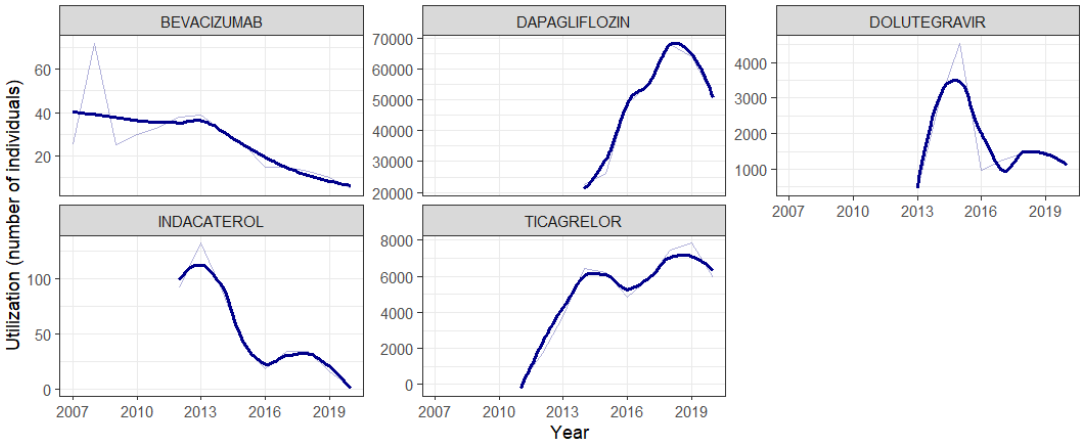
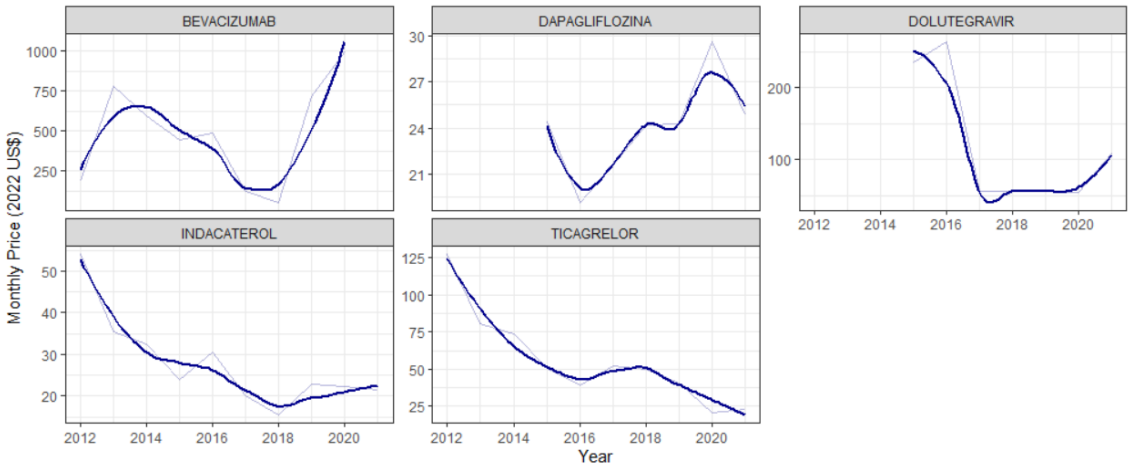
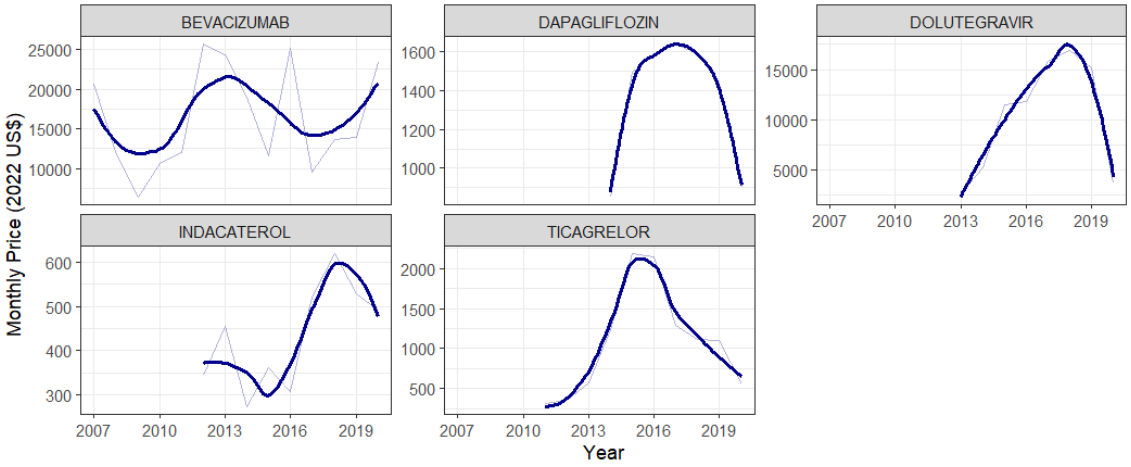


Figure A3. Monthly Price Slopes by Product

a. Colombian slopes



b. US slopes



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