Factors Influencing Access to Essential Medicines in Low- and Middle-Income Countries: A Quantitative Analysis of 72 Medicines

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Abstract

Background: Access to essential medicines is an important challenge worldwide, with low- and middle-income countries accounting for the majority population without access to essential medicines. Using the diffusion of innovations framework, this research examines the effects of medicine-, country-, and company-level factors on access to essential medicines centrally authorized in the EU.

Methods: This study contains a cross-sectional examination of 72 essential medicines authorizations in 8 LMICs. Logistic regressions were conducted to determine the impact of medicine- and company-level factors. Kendall's tau non-parametric correlation was used to determine the relationship of local medicine authorizations to country-level factors.

Results: Access to essential medicines centrally authorized in the EU varied across LMICs. Medicine- and company-level factors were significant predictors of authorizations, while country-level factors correlated with different essential medicine authorizations in LMICs – results varied on a country-by-country basis and no factor alone could explain differences in access to medicines in LMICs.

Conclusion: Differences in access to essential medicines in Europe vs LMICs, as well as between LMICs, is alarming an indicative of future research to better understand this problem. Future research should explore additional medicine-, country-, and company-level factors, and delays experienced in access to medicine to gain a full understanding of diffusion of essential medicines in LMICs.

Keywords: essential medicines, diffusion of medicines, low- and middle-income countries (LMICs), medicine access, essential medicines list (EML)

Introduction

Approval by a national medicines regulatory body is an important first step in ensuring patients in low- and middle-income countries (LMICs) have access to essential medicines. The World Health Organization (WHO) defines essential medicines as medicines which satisfy the priority health needs of the population (WHO, 2021). Medicines which hold that title can be found in the Essential Medicines List (EML), a WHO list containing medications which are deemed effective and safe to meet important healthcare needs worldwide (WHO, 2021). Despite their importance, access to essential medicines worldwide is limited to *at best* 49% of the population (WHO, 2021, p.2). Of said 49%, the populations of lowest-income countries still lag far behind that of high-income countries (HICs), with middle-income countries accounting for the largest absolute population lacking coverage of essential health services (including essential medicines) in 2017 (WHO, 2021, p. 2). Lack of access to essential medicines is associated with, among others, prolonged illness, development of chronic conditions, increased mortality rates, and increased likelihood of poverty, thus posing an important problem to LMICs (McIntyre, 2006; Weil, 2014). Evidence suggests that lack of access to medicines can be attributed to the absence of marketing authorization for new/existing medicines in LMICs, indicating the necessity to further understand barriers faced by regulatory agencies in LMICs to improve access to essential medicines (Eichler et al., 2013; Narsai & Mantel-Teeuwisse, 2012; Nwokike et al., 2015).

The existing literature on access to medicines contains important findings. First, research on the diffusion of medicines (i.e., its use in a country's national health system) indicates that the price of medicines play an important role in medicine access, with higher-cost medicines having lower rates of access (Cameron et al., 2009, p.240). Medicine cost is often associated with

medicine size: biologic (larger) medicines are derived from living cells or biological processes, whereas small molecule (smaller) medicines are made by chemical synthesis and are often less costly than their larger counterparts (Projan et al., 2004; Makurvet, 2021). Biologic medicines are often used to treat cancer, and other non-communicable diseases (NCDs) which although prevalent in LMICs are often neglected (Makurvet 2021; Islam et al., 2014; Boutayeb & Boutayeb, 2005). Despite the presence of NCDs in LMICs, access to medicines for NCDs remains low in LMICs, as LMICs focus primarily on access to medicines for infectious diseases (Mattke et al., 2011). Essential medicines are meant to be accessible to all, however the literature does not indicate whether the nature of the medicine or its use (i.e., the illness/disease/disorder the medicine treats) predict differences in access to medicines.

Secondly, the literature suggests that cross-country variance in access to pharmaceuticals can be explained by country-level factors –countries with higher GDP and health expenses (HE) have access to more medicines (Brekke et al., 2014). These findings are supported by earlier work comparing the diffusion of medicines in HICs vs LMICs (Desiraju et al., 2004). The availability of financing is thus essential to countries' decisions to market their medicine in a given market. Notably, current research has primarily focused on HICs, not LMICs (Brekke et al., 2014; Costa-Font et al., 2015; Desiraju et al., 2004; Md Hamzah & See, 2021). New medicines are marketed in HICs (e.g., United States or European Union), before (if ever) they are marketed in LMICs, explaining the bias in the literature (Kremer, 2002; Cockburn et al., 2014). This occurs even in cases where the medicine is clinically tested and needed in LMICs (Limaye et al., 2015). It is therefore impossible to draw conclusions on factors affecting medicine diffusion in LMICs based on the current literature which focuses primarily on HICs, as LMICs are characterized by different financial, regulatory, and medical challenges.

Finally, the limited studies on the diffusion of medicines in LMICs has primarily focused on the role played by regulatory agencies. Research in Latin America has demonstrated the impact of the EMA and FDA on regulatory decisions made by Latin American countries, illustrating the international impact of regulatory decisions (Durán et al., 2021). Furthermore, research in South Africa indicated that different regulatory requirements across Africa posed important challenges to medicine marketing authorization across countries (Narsai & Mantel-Teeuwisse, 2012). By focusing primarily on national regulatory processes, the current literature generally does not account for the fact that for diffusion of medicines to occur, a company's (or other rights holder's) decision to market said medicine in LMIC market. Little is known about the impact of company characteristics (e.g., company size, or its presence in the LMIC market) may influence access to medicines in LMICs. These factors are relevant and described in the business literature on company behaviour yet are absent in the global public health literature on access to medicines (Trim & Pan, 2005). It is thus difficult to determine the range of factors (relating to the medicine, the LMIC market, and the company) influencing access to medicines in LMICs, as well as whether such factors are interlinked.

The overall aim of this study is to determine the factors associated with access to medicines in LMICs, using public information from regulatory agency websites and the WHO. This exploratory study will more specifically focus on the theory of diffusion of innovations proposed by Rogers et al. (2014), while considering three characteristics proposed by Bonair and Persson: (1) traits of an innovation (i.e., medicine characteristics); (2) traits of the actors (i.e., company characteristics); and (3) traits of the environment (i.e., country characteristics), which are explained in detail below (cited in Md Hamzah & See, 2021). This theory provides a basis upon which a new model will be built explaining factors influencing access to medicines in

LMICs. Understanding the role of each factor is essential to re-thinking and re-establishing incentives for making available needed medicines for people in LMICs.

Theoretical Background

Rogers' (2014) theory of diffusion of innovations proposes that diffusion can be illustrated by a *S*-curve shape characterized by time (*x-axis*) and adoption (*y-axis*), containing a

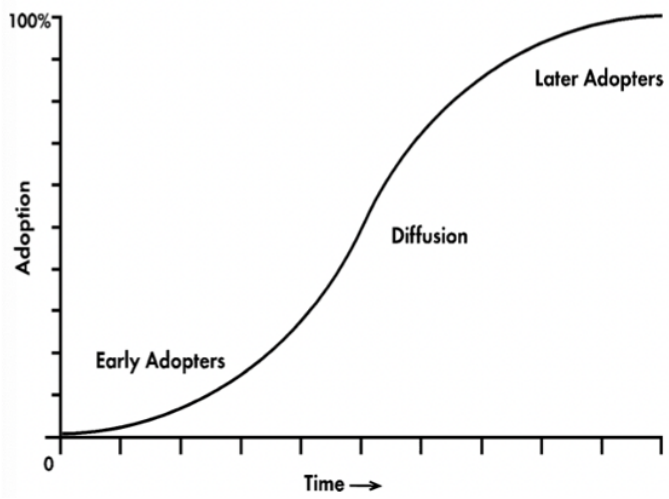

***Figure 1**: Diffusion of Innovation Theory (Dearing, 2018, p.100)*

low number of early adopters, followed by a higher early majority, an equally high late majority, and a low number of laggards (see **Figure 1**). More importantly, the theory claims that different factors affect both time and adoption (Rogers et al., 2014). Later, Bonair and Persson built upon Rogers' work by identifying three factors which applied particularly to the diffusion of medicines: (1) traits of an innovation (i.e., new drug); (2) traits of the actors (i.e., companies); and (3) traits of the environment (i.e., countries) (cited in Md Hamzah & See, 2021).

The use of the theory of diffusion of innovations, including the contributions of Bonair and Persson, has often been used in public health to explain the uptake of new health products, including medicines, within hospitals, communities, and countries (Chauhan & Mason, 2008; Mason, 2008; Md Hamzah & See, 2021). Nonetheless, some have criticized it for its assumption

(reflected in its *S*-curve shape) that an innovation may ever be adopted by all (Oldenburg & Glanz, 2008). In the case of essential medicines, however, the ideal scenario is one in which all countries have access to all essential medicines. As such, this theory provides a framework for the formulation of hypotheses that this study can statistically test.

Below, I tailor this theory to the case of regulatory approval of essential medicines by relating the three factors to important aspects of pharmaceutical regulation. By doing this, I can establish key hypotheses that I test in this research.

Research Question

The previous sections of this paper highlighted the potential relationship between medicine-, country-, and company-level factors on access of new essential pharmaceuticals in LMICs. The current study thus aims to answer two questions: (1) *Are essential medicines (centrally) authorized in the EU also licensed in LMICs?*; (2) *Which factors are associated with the local market approval of essential medicines in LMICs?* This study explores medicine-, country-, and company-level factors.

Medicine-Level Factors

Medicine characteristics are expected to influence the number of countries authorizing said medicine. The nature of the medicine itself (i.e., medicine size) is associated with additional regulatory constraints (Sangeetha et al., 2022). Given the nature of biologics, biologic medicines are associated with higher costs than small molecule medicines, as well as additional regulatory barriers, potentially hindering patient access to biologic medicines (Sangeetha et al., 2022). Biologic medicines and small molecule medicines continue to coexist in the EML as, despite

their differences in costs, both medicine sizes are essential to treat a variety of conditions. To account for differences in costs, EML medicines are categorized as core items, or complementary items. Core EML items are medicines considered most cost-effective, often needing little to no additional resources to be implemented or used (WHO, n.d.). Complementary EML items are medicines which require additional diagnostic or monitoring facilities, and/or specialized medical care (WHO, n.d.). The EML thus attempts to account for differences in costs and implementations by designating the medicines as either core, or complementary items. Finally, the EML is also organized by treatment category, grouping together medicines which treat similar conditions/medicines which have similar areas of treatment (e.g., category 6 is composed of anti-infective medicines; category 17 is for gastrointestinal medicines) (WHO, n.d.). Thus, treatment category, as defined by the EML, may influence a medicine's adoption in LMICs as LMICs have a higher burden of infectious diseases than HICs, indicating a larger need for anti-infective medicines (Boutayeb & Boutayeb, 2005).

Country-Level Factors

Country characteristics are expected to influence the number of countries authorizing different medicines. Population size is an important country-level factor as it represents the number of people that could necessitate a certain medication. As such, larger LMICs, as defined by their population size, are expected to have access to more essential medicines than smaller LMICs as they represent a larger potential market for companies marketing such medicines (Trim & Pan, 2005). Medicine access may however remain limited in countries where out-of-pocket (OOP) costs for medicines (i.e., the cost of medicines not reimbursed by insurance) are high, due to a country's healthcare coverage. If a medicine's usage is limited by the costs it

imposes on patients, a country's market may be less attractive to pharmaceutical companies, which may not apply for regulatory approval of medicines within such countries. In contrast, higher national HE are expected to be associated with higher levels of medicine access, as it is associated with increased use of essential health services (including essential medicines) (WHO, 2021).

Company-Level Factors

Company characteristics are expected to impact different types of medicine authorizations in LMICs. A company's size, defined by the total number of essential medicine authorizations held by the company across different countries, may influence the types of essential medicines marketed in LMICs by such companies. Medicines marketed by larger companies may be more likely to be biologic medicines, or complementary items, as those are associated with higher costs, which larger companies are more likely to afford than smaller companies (Brekke et al., 2014). Furthermore, evidence suggests that companies face important barriers when entering new countries (Narsai & Mantel-Teeuwisse, 2012). As such, a medicine marketed by a company which is already present in a LMIC may be more likely to be biologic or complementary as the company is more familiar with regulations imposed by national regulatory agencies, and thus better able to navigate such regulatory requirements.

This research examines which and how may essential medicines centrally authorized in the EU are also authorized in LMICs. References in the hypotheses to medicines means "essential medicines centrally authorized in the EU." Based on existing research and the theoretical framework described above, the following hypotheses are formulated:

H1: Medicines authorized in the EU are not authorized in LMICs (WHO, 2021)

H2: Medicine-level factors are significant predictors of the total number of medicines approved in LMICs.

H2a: Small molecule medicines are more likely to be authorized in LMICs than biologic medicines (Sangeetha et al., 2022).

H2b: Core essential medicines are more likely to be authorized in LMICs than complementary medicines (WHO, n.d.)

H2c: Anti-infective medicines are more likely to be authorized in LMICs than other categories of medicines (Boutayeb & Boutayeb, 2005).

H3: Country-level factors are associated with the authorization of medicines in LMICs.

H3a: LMICs with large populations have more authorized medicines (than LMICs with small populations) (Trim & Pan, 2005).

H3b: LMICs with high OOP HE per capita have fewer authorized medicines than LMICs with low OOP HE per capita (WHO, 2021).

H3c: LMICs with high total HE per capita have more authorized medicines than LMICs with low HE (WHO, 2021).

H4: Company size is a significant predictor of medicine authorization types (defined by medicine-level factors) in LMICs.

H4a: Larger companies are more likely to market biologic medicines than smaller companies (Brekke et al., 2014; Projan et al., 2004)

H4b: Larger companies are more likely to market complementary items than smaller companies (Brekke et al., 2014; WHO, n.d.).

H4c: Larger companies are more likely to market anti-infective medicines than smaller companies (Brekke et al., 2014, Boutayeb & Boutayeb, 2005).

H5: Company presence is a significant predictor of medicine authorization types (defined by medicine-level factors) in LMICs.

H5a: Companies that are already present in a LMIC are more likely to market biologic medicines than companies which are not already present (Trim & Pan, 2005; Sangeetha et al., 2022)

H5b: Companies that are already present in a LMIC are more likely to market complementary medicines than companies which are not already present (Trim & Pan, 2005; WHO, n.d.)

H5c: Companies that are already present in a LMIC are more likely to market immunomodulators and antineoplastics than companies which are not already present (Trim & Pan, 2005; Sangeetha et al., 2002).

Methods

Study Design

This is a cross-sectional analysis of the approval of medicines centrally licensed in the EU and the factors affecting their approval in 8 LMICs, using data from the European Medicines Agency (EMA), the WHO, as well as national pharmaceutical regulatory agencies. The LMICs selected for analysis are Brazil, Colombia, Ecuador, Philippines, South Africa, Tanzania, Tunisia, and Uganda. This design provides an ideal snapshot of the current status of medicines approval, which is the first step towards patient access, in LMICs.

The advisory committee for this project consisted of Prof. Dr. Aukje-Mantel-Teeuwisse (Utrecht University/WHO Collaborating Centre for Pharmaceutical Regulation and Policy) and

Dr. Carlos Durán (Utrecht Medical Centre/former essential medicines committee member in Ecuador).

Sample

Medicines were selected for analysis based on their addition to the WHO's Essential Medicines List (EML) from 2002 to 2019, resulting in 228 total new additions. The start point was selected as in 2002, the WHO updated the process of medicine selection for the EML, allowing expensive but effective medicines to be added to the list (Hogerzeil, 2004). Medicines which were previously absent due to high prices, such as antiretroviral medicines for HIV/AIDS, were now present on the EML irrespective of their cost. The addition of a medicine to the list now implies that these medicines should become affordable (i.e., accessible) to all those who need them (Hogerzeil, 2004).

We opted to examine medicines which were centrally authorized by the EMA, as evidence suggests that companies first market medicines in HICs prior to LMICs (Kremer, 2002; Cockburn et al., 2014). This was furthermore recommended by the advisory committee, given evidence suggesting that the pharmaceutical markets of HICs and LMICs are connected (Perehudoff et al., 2021; Durán et al., 2021).

Countries were selected based on the principle of most representative of different levels of development, as determined by the World Bank. As such, we included countries which qualified under different levels of income between lower-income (e.g., Uganda) and upper-middle income (e.g., Brazil and South Africa), across three regions: Africa, Asia, and Latin America.

Country-selection was based on information provided by their regulatory websites. We included only LMICs with websites that contained: medicine marketing authorization status (i.e., is the use of this medicine authorized in this country?), and medicine marketing authorization holder (i.e., which company is authorized to market this medicine in this country?). Countries which did not provide this information were thus excluded from the study. In case of multiple marketing authorization holders, companies with the earliest marketing authorization were selected as they were deemed to be penetrating the market. Furthermore, to ensure accuracy of data collection, only countries with regulatory websites in English, French, Spanish, and Portuguese were included, as I do not speak other languages.

Data Collection

First, we consulted the WHO's EML from 2002 to 2019, and corresponding reports illustrating and justifying the changes each new list has undergone (i.e., whether medicines were added/deleted, or experienced changes in dosages (WHO, n.d.). Using these reports, we compiled a list of all new additions to the EML occurring from 2002 to 2009 (excluding dosage changes), while accounting for treatment categories, core/complementary status, and medicine size.

Second, we identified the WHO essential medicines that were centrally approved using the EMA website (EMA, n.d.). Data was collected for the medicines with the same international non-proprietary name (INN) and dosage form on the WHO EML, as well as the brand name of the pharmaceutical within the EU, and the name of the market authorization holder (usually a pharmaceutical company). Medicines which were not centrally authorized within the EU were excluded from the study. This data then collected from the LMICs included in the study.

Descriptive Data Analysis

To answer the first research question, a cross-table was created, illustrating the total number of essential medicine authorizations (for medicines centrally authorized in the EU) for all LMICs within our selection. Crosstabulations allow for the simultaneous examination of the distributions of authorizations for medicine-level factors across different countries, and is therefore the ideal tool to determine whether essential medicine authorizations vary across LMICs (Cooksey, 2020). Furthermore, we determined the mean and standard deviation for each factor to obtain a more complete descriptive summary of the dataset (Cooksey, 2020)

Statistical Data Analysis

To determine the significance of medicine-level factors as predictors of the number of essential medicine authorizations for each country, binary logistic regressions were conducted with each individual factor (i.e., medicine type, EML item type, and EML category) as predictors. An additional logistic regression was conducted with all factors combined as predictors.

To determine the significance of country-level factors, we conducted a Kendall's tau non-parametric correlational analysis of population size, current HE, OOP HE, and total number of essential medicine authorizations. We further conducted correlational analyses to determine whether there was a relationship between country-level factors and different types of authorizations defined by medicine size, core/complementary status, and treatment category. Kendall's tau was chosen as it is best suited for small samples with a wide range of values, as we only included 8 countries in the analysis (Field, 2013).

To determine the significance of company-level factors as predictors of the types of essential medicine authorizations for each country (defined by medicine-level factors), logistic regressions were conducted with each individual factor (i.e., company size, company presence) as predictors. An additional logistic regression was conducted with all factors combined as predictors.

Additional information regarding variables and statistical analyses can be found in Appendix 1.

Results

References in the results to medicines means "essential medicines centrally authorized in the EU between 2002-2019."

A total of 72 medicines were included in this study. Medicines in the sample were most often core medicines (60%), and small molecule medicines (79%), with anti-infective medicines and immunomodulators and antineoplastics accounting for the leading treatment categories (49% and 29%, respectively) (**Table 1**).

Table 1: Medicine-Level Factors per Country

		Low- and Middle-Income Countries							
		Latin America			Asia	Africa			
	EU	Brazil	Colombia	Ecuador	Philippines	South Africa	Tanzania	Tunisia	Uganda
Medicine Factors	(n = 72)	(n = 59)	(n = 55)	(n = 51)	(n = 52)	(n = 19)	(n = 48)	(n = 42)	(n = 40)
Total Authorizations, *% of EU (n)*	100 (72)	82 (59)	76 (55)	71 (51)	72 (52)	26 (19)	67 (48)	58 (42)	56 (40)
EML Item Type, *% (n)*									
Core Items	60 (43)	58 (34)	56 (31)	57 (29)	54 (28)	58 (11)	58 (28)	50 (21)	73 (29)
Complementary Items	40 (29)	42 (25)	44 (24)	43 (22)	46 (24)	42 (8)	42 (20)	50 (21)	27 (11)
Medicine Type, *% (n)*									
Small Molecule	79 (57)	78 (46)	80 (44)	79 (40)	79 (41)	84 (16)	83 (40)	79 (33)	85 (34)
Biologic	21 (15)	22 (13)	20 (11)	21 (11)	21 (11)	16 (3)	17 (8)	21 (9)	15 (6)
EML Category, *% (n)*									
Anti-infective medicines	49 (35)	46 (27)	44 (24)	43 (22)	40 (21)	42 (8)	48 (23)	36 (15)	50 (20)
Immunomodulators and antineoplastics	29 (21)	32 (19)	33 (18)	33 (17)	35 (18)	42 (8)	31 (15)	38 (16)	25 (10)
Other	22 (16)	22 (13)	23 (13)	24 (12)	25 (13)	16 (3)	21 (10)	16 (11)	25 (10)

Access to Essential Medicines in LMIC

A description of authorizations of medicines in LMICs, as well as an initial examination of the distribution of authorizations among medicine factors can be found in **Table 1**. This table illustrates that 26-82% of 72 medicines were authorized/recommended within our selection of LMICs. Medicines authorized within all 8 countries included 1 anti-epileptic, 3 immunomodulators and antineoplastics, and 4 anti-infectives. Authorized medicines were more frequently core EML items (mean = 58.3%, sd = 6%), and small molecule medicines (mean = 81.1%, sd = 3%). Anti-infective medicines and immunomodulators and antineoplastics accounted for most authorizations, with "other" treatment categories accounting for, at most, 25% of authorizations. **Figure 2** illustrates the distribution of essential medicines included in our sample per treatment category.

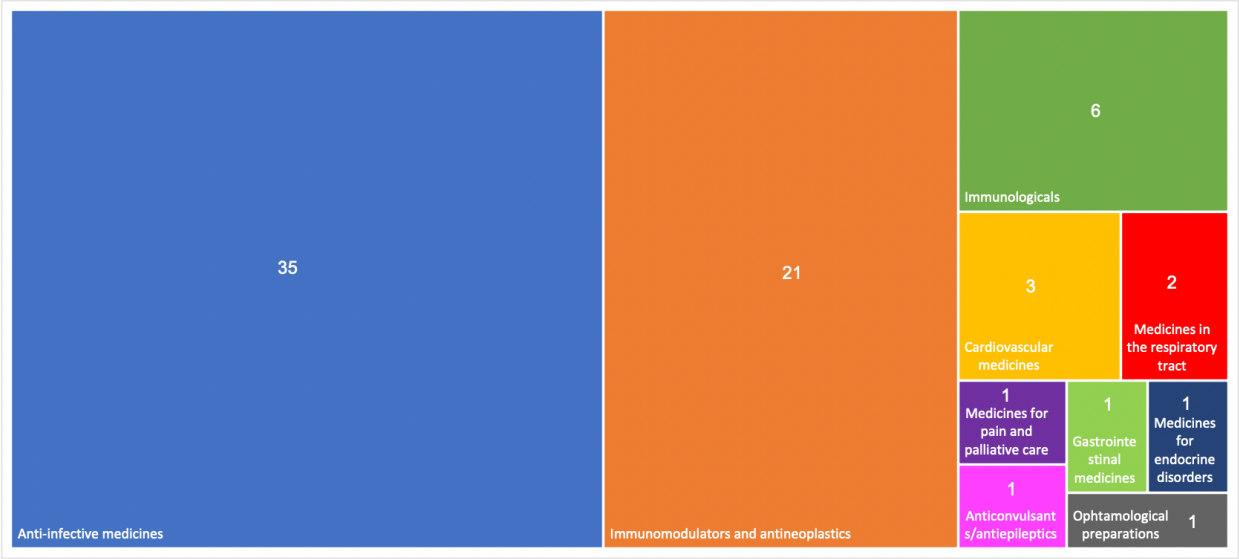

Figure 2: Medicine Authorizations per EML Category for the Sample of 72 Medicines

Medicine-Level Factors

Table 2 illustrates the results of the logistic regression analyses of medicine-level factors as predictors for the number of medicine authorizations within each LMIC. The individual

effects of medicine size and treatment category were not significant for any of the LMICs within the selection. In the model accounting for all medicine-level factors, anti-infective medicines were less likely to be authorized in Tunisia than immunomodulators and antineoplastics, or other medicines (OR = 0.207, 95%CI = 0.05-0.94) but not in other LMICs.

Core/complementary status was only a significant predictor of medicine authorizations in Uganda, with core items being more likely to be authorized than complementary EML items (OR = 3.390, 95%CI = 1.27-9.07). This finding was exacerbated when all medicine-level factors were included in the model, with core items being 13.75 times more likely to be authorized than complementary EML items (OR = 13.745, 95%CI = 1.50-125.6). Core/complementary status was not a significant predictor of authorizations for any other country.

Table 2: Logistic Regression Model of Medicine-Level Predictors of Essential Medicine Authorizations in LMICs

	Latin America						Asia	
	Brazil (n = 59)		Colombia (n = 55)		Ecuador (n = 51)		Philippines (n = 52)	
Factors in the Model	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**
Core/Complementary Status								
Core EML	0.604	(0.17-2.19)	0.538	(0.17-1.74)	0.659	(0.23-1.91)	0.389	(0.12-1.23)
Complementary EML	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Medicine Size								
Small Molecule	1.554	(0.31-7.91)	0.813	(0.22-2.98)	0.536	(0.16-1.76)	1.073	(0.30-3.87)
Biologic	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Treatment Category								
Anti-infective medicines	0.741	(0.18-3.43)	0.503	(0.24-7.99)	0.564	(0.15-2.12)	0.346	(0.08-1.44)
Immunomodulators and antineoplastics	0.424	(0.32-15.00)	1.385	(0.24-7.98)	1.412	(0.30-6.81)	1.39	(0.24-7.99)
Other	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
All Medicine-Level Factors								
Core EML	1.283	(0.22-7.60)	0.698	(0.12-4.25)	0.983	(0.19-5.14)	0.481	(0.08-2.94)
Complementary EML	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Small Molecule	1.348	(0.20-8.91)	0.366	(0.07-1.98)	0.222	(0.45-1.101)	0.248	(0.07-2.00)
Biologic	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Anti-infective medicines	0.901	(0.17-4.91)	0.285	(0.05-1.75)	0.241	(0.04-1.38)	0.192	(0.03-1.17)
Immunomodulators and antineoplastics	2.901	(0.23-26.07)	0.810	(0.07-9.64)	1.012	(0.11-9.55)	0.579	(0.05-7.10)
Other	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref

***Significant Predictor**

Table 2: Logistic Regression Model of Medicine-Level Predictors of Essential Medicine Authorizations in LMICs (cont.)

	Africa							
	South Africa (n = 19)		Tanzania (n = 48)		Tunisia (n = 42)		Uganda (n = 40)	
Factors in the Model	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**
Core/Complementary Status								
Core EML	0.902	(0.31-2.62)	0.840	(0.31-2.30)	0.364	(0.13-1.0)	**3.390***	(1.27-9.07)
Complementary EML	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Medicine Size								
Small Molecule	0.641	(0.16-2.57)	0.486	(0.15-1.55)	1.091	(0.34-3.48)	0.451	(0.14-1.44)
Biologic	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Treatment Category								
Anti-infective medicines	1.284	(0.29-5.66)	1.150	(0.34-3.93)	0.341	(0.10-1.19)	0.800	(0.24-2.70)
Immunomodulators and antineoplastics	2.667	(0.58-12.36)	1.500	(0.38-6.00)	1.455	(0.34-6.25)	0.545	(0.15-2.05)
Other	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
All Medicine-Level Factors								
Core EML			1.003	(0.20-4.98)	0.450	(0.09-2.31)	**13.745***	(1.50-125.6)
Complementary EML	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Small Molecule			0.392	(0.10-1.55)	0.417	(0.10-1.76)	0.348	(0.08-1.54)
Biologic	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Anti-infective medicines			0.721	(0.17-3.09)	**0.207***	(0.05-0.94)	0.498	(0.10-2.44)
Immunomodulators and antineoplastics			1.24	(0.16-9.50)	0.549	(0.07-5.11)	4.154	(0.34-51.38)
Other	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref

***Significant Predictor**

Country-Level Factors

A descriptive illustration of country-level factors per country can be found in **Table 3**. The population size varies widely in the sample of LMICs, with Brazil representing the largest LMIC, and Tunisia representing the smallest. HE also varied widely with Brazil accounting for the highest HE per capita, and Uganda the lowest.

Table 4 provides the results of the Kendall's tau nonparametric correlation for the country-level factors and authorization data. Population size is positively correlated with small molecule medicines (Kendall's tau = 0.592, $p = 0.28$). HE are positively correlated with complementary, biologic immunomodulators and anti-neoplastic medicines (Kendall's tau = 0.535, $p = 0.46$; Kendall's tau = 0.551, $p = 0.43$; Kendall's tau = 0.535, $p = 0.46$, respectively). OOP HE are more strongly correlated with these medicines (Kendall's tau = 0.592, $p = 0.28$;

Kendall's tau = 0.667, $p = 0.14$; Kendall's tau = 0.592, $p = 0.28$, respectively). OOP HE are additionally positively correlated with the total number of authorizations per country (Kendall's tau = 0.556, $p = 0.37$) and the number of "other" authorizations (Kendall's tau = 0.589, $p = 0.32$).

Table 3: Country-Level Factors per Country

		Low- and Middle-Income Countries							
		Latin America			Asia	Africa			
Medicine Factors	**EU** (N = 72)	**Brazil** (N = 59)	**Colombia** (N = 55)	**Ecuador** (N = 51)	**Philippines** (N = 52)	**South Africa** (N = 19)	**Tanzania** (N = 48)	**Tunisia** (N = 42)	**Uganda** (N = 40)
Total Authorizations, *% of EU (n)*	100 (72)	82 (59)	76 (55)	71 (51)	72 (52)	26 (19)	67 (48)	58 (42)	56 (40)
Country Characteristics									
Population Size	447,479,493	212,559,409	50,882,884	17,643,060	109,581,085	59,308,690	59,734,213	11,818,618	45,741,000
Health Expenses* (per capita)	$ 3,476.43	$ 853.39	$ 495.33	$ 486.49	$ 142.08	$ 546.69	$ 40.34	$ 233.06	$ 32.41
Out of Pocket Health Expenses* (per capita)	$ 538.85	$ 212.32	$ 73.61	$ 150.23	$ 68.99	$ 31.11	$ 8.94	$ 88.42	$ 12.40

** in USD*

Table 4:Correlations Between Country-Level Factors and Authorizations per Country

	Population Size	**Current Health Expenses per capita**	**Out of Pocket Health Expenses per capita**
Medicine Factors			
Total Authorizations	.500	.500	**.556***
Core/Complementary status			
Core Items	.400	.343	.514
Complementary Items	.479	**.535***	**.592***
Medicine Size			
Small Molecule	**.592***	.423	.429
Biologic	.435	**.551***	**.667***
Treatment Category			
Anti-infective medicines	.500	.389	.444
Immunomodulators and antineoplastics	.479	**.535***	**.592***
Other	.412	.471	**.589***

** Correlation is significant at the 0.05 level (2-tailed)*

Company-Level Factors

Table 5 provides a descriptive analysis of medicine access, medicine-level factors, and per market authorization holder presence. Company number represents the number of companies marketing medicines within each country. Different companies market different quantities of

medicines within each country, resulting in varying quantities of companies per country. In the EU, for example, 39% of companies marketing medicines are “not present” while 61% are “present.” Authorizations in the EU 19% (14) are held by “not present” companies while 81% (58) are held by “present” companies. For all countries, companies which are already “present” in the local market hold most marketing authorizations. This finding remains true even for countries where there are a larger proportion of “not present” companies, than “present” companies.

“Present” companies hold most marketing authorizations for core medicines in all countries. The same is true for complementary medicines in all countries except the Philippines.

Small molecule and biologic medicine authorizations are primarily held by companies which are “present” in LMICs for all countries.

For all countries, anti-infective medicine authorizations are most frequently held by “present” companies in LMICs. “Present” companies hold most medicine authorizations for immunomodulators and antineoplastics for all countries except the Philippines. “Other” medicine authorizations are most frequently held by “present” companies in all countries except Colombia, Ecuador, South Africa, and Uganda.

Table 5: Company-Level Factors per Country

	Latin America								Asia	
	EU (n = 72)		Brazil (n = 59)		Colombia (n = 55)		Ecuador (n = 51)		Philippines (n = 52)	
	Not Present	Present	Not Present	Present	Not Present	Present	Not Present	Present	Not Present	Present
Medicine Access, % (n)										
Companies, % (n companies)	39 (11)	**61 (17)**	**54 (15)**	46 (13)	**65 (20)**	35 (11)	47 (15)	**53 (17)**	**58 (19)**	42 (14)
Authorizations, % (n)	19 (14)	**81 (58)**	25 (15)	**75 (44)**	18 (10)	**81 (45)**	43 (22)	**57 (29)**	44 (23)	**56 (29)**
Medicine Factors, % (n)										
Core/Complementary Status										
Core Items	14 (6)	**86 (37)**	27 (9)	**73 (25)**	42 (10)	**58 (14)**	48 (14)	**52 (15)**	29 (8)	**71 (20)**
Complementary Items	28 (8)	**72 (21)**	24 (6)	**76 (19)**	32 (10)	**68 (21)**	36 (8)	**64 (14)**	**63 (15)**	37 (9)
Medicine Size										
Small Molecule	19 (11)	**81 (46)**	22 (10)	**78 (36)**	36 (16)	**67 (28)**	43 (18)	**57 (24)**	44 (18)	**56 (23)**
Biologic	20 (3)	**80 (12)**	38 (5)	**62 (8)**	36 (4)	**67 (7)**	44 (4)	**56 (5)**	46 (5)	**54 (6)**
Treatment Category										
Anti-infective medicines	11 (4)	**89 (31)**	22 (6)	**78 (21)**	21 (5)	**79 (19)**	27 (6)	**73 (16)**	29 (6)	**71 (15)**
Immunomodulators and antineoplastics	29 (6)	**71 (15)**	21 (4)	**79 (15)**	44 (8)	**56 (10)**	41 (7)	**59 (10)**	**61 (11)**	39 (7)
Other	25 (4)	**75 (12)**	39 (5)	**61 (8)**	**54 (7)**	46 (6)	**75 (9)**	25 (3)	46 (6)	**54 (7)**

Table 5: Company-Level Factors per Country (cont.)

	Africa							
	South Africa (n = 19)		Tanzania (n = 48)		Tunisia (n = 42)		Uganda (n = 40)	
	Not Present	Present	Not Present	Present	Not Present	Present	Not Present	Present
Medicine Access, % (n)								
Companies, % (n companies)	31 (9)	**69 (12)**	33 (8)	**67 (16)**	33 (8)	**67 (16)**	38 (8)	**62 (13)**
Authorizations, % (n)	47 (9)	**53 (10)**	23 (11)	**77 (37)**	24 (10)	**76 (32)**	33 (13)	**67 (27)**
Medicine Factors, % (n)								
Core/Complementary Status								
Core Items	46 (5)	**54 (6)**	21 (6)	**79 (22)**	29 (6)	**71 (15)**	38 (11)	**62 (18)**
Complementary Items	**50 (4)**	**50 (4)**	25 (5)	**75 (15)**	19 (4)	**81 (17)**	18 (2)	**82 (9)**
Medicine Size								
Small Molecule	**50 (8)**	**50 (8)**	23 (9)	**77 (31)**	21 (7)	**79 (26)**	29 (10)	**71 (24)**
Biologic	33 (1)	**67 (2)**	25 (2)	**75 (6)**	33 (3)	**67 (6)**	**50 (3)**	**50 (3)**
Treatment Category								
Anti-infective medicines	25 (2)	**75 (6)**	17 (4)	**83 (19)**	20 (3)	**80 (12)**	20 (4)	**80 (16)**
Immunomodulators and antineoplastics	**50 (4)**	**50 (4)**	13 (2)	**87 (13)**	25 (4)	**75 (12)**	20 (2)	**80 (8)**
Other	**100 (3)**	0 (0)	**50 (5)**	**50 (5)**	27 (3)	**73 (8)**	**70 (7)**	30 (3)

Tables 6a and **6b** illustrate the result of the logistic regression analyses for country-level factors as predictors of different medicine authorization types. In the Philippines, core items were more likely to be marketed by "present" companies, and the odds were exacerbated in a

model accounting for all company-level factors (OR = 4.167, 95%CI = 1.30-13.35; OR = 5.363, 95%CI = 1.34-21.42, respectively). In Colombia, Ecuador, and Uganda, anti-infective medicines were less likely to be marketed by "present" companies (OR = 0.226, 95%CI = 0.05-0.98; OR = 0.125, 95%CI = 0.03-0.62; OR = 0.107; 95%CI = 0.01-0.84). In Uganda, this finding also applied to immunomodulators and antineoplastics (OR = 0.107, 95%CI = 0.02-0.61). The effects of company presence as a significant predictor of treatment categories were reduced once a model with all variables was included for Ecuador (OR = 0.021, 95%CI = 0.00-0.40), whereas it was eliminated for Colombia and Uganda. In Brazil, Tunisia, and Uganda, "present" companies were slightly less likely to market biologic medicines in Brazil, Tunisia, and Uganda (OR = 0.001; 95%CI = 0.00-0.17; OR > 0.000, 95%CI = 0.00-0.17; OR = 0.005, 95%CI = 0.00-0.41).

Table 6a: Logistic Regression Model of Individual Company-Level Factors as Predictors of Core/Complementary Status, Medicine Size, and Treatment Category

	Latin America						Asia	
	Brazil (n = 59)		Colombia (n = 55)		Ecuador (n = 51)		Philippines (n = 52)	
Factors in the Model	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**
Company Presence								
Present								
Core/Complementary Status								
Core EML	0.877	(0.27-2.89)	1.500	(0.50-4.54)	0.612	(0.20-1.90)	**4.167***	(1.30-13.35)
Complementary EML	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Medicine Size								
Biologic	0.444	(0.12-1.67)	1.000	(0.25-3.95)	0.938	(0.22-4.00)	0.939	(0.25-3.58)
Small Molecule	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Treatment Category								
Anti-infective medicines	0.457	(0.11-1.93)	**0.226***	(0.05-0.98)	**0.125***	(0.03-0.62)	0.467	(0.11-1.98)
Immunomodulators and antineoplastics	0.427	(0.09-2.05)	0.686	(0.16-2.87)	0.233	(0.46-1.19)	1.833	(0.43-7.77)
Other	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Not Present = Reference								
Total Authorizations *(per company)*								
Core/Complementary Status								
Core EML	0.991	(0.94-1.04)	1.029	(0.97-1.09)	0.956	(0.90-1.01)	1.017	(0.96-1.08)
Complementary EML	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Medicine Size								
Biologic	1.060	(0.99-1.13)	1.040	(0.97-1.12)	**1.080***	(1.00-1.16)	1.028	(0.96-1.10)
Small Molecule	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Treatment Category								
Anti-infective medicines	0.986	(0.93-1.05)	1.055	(0.98-1.14)	1.019	(0.95-1.10)	0.987	(0.92-1.06)
Immunomodulators and antineoplastics	1.014	(0.95-1.09)	1.014	(0.94-1.10)	1.030	(0.96-1.11)	0.923	(0.85-1.01)
Other	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref

***Significant Predictor**

Table 6a: Logistic Regression Model of Individual Company-Level Factors as Predictors of Core/Complementary Status, Medicine Size, and Treatment Category (cont.)

	Africa							
	South Africa (n = 19)		Tanzania (n = 48)		Tunisia (n = 42)		Uganda (n = 40)	
Factors in the Model	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**
Company Presence								
Present								
Core/Complementary Status								
Core EML	1.200	(0.19-7.44)	1.222	(0.32-4.74)	0.588	(0.14-2.49)	0.364	(0.07-2.00)
Complementary EML	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Medicine Size								
Biologic	2.000	(0.15-26.73)	0.871	(0.15-5.08)	0.538	(0.11-2.72)	0.417	(0.07-2.43)
Small Molecule	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Treatment Category								
Anti-infective medicines			0.211	(0.04-1.09)	0.667	(0.11-4.17)	**0.107***	(0.01-0.84)
Immunomodulators and antineoplastics			0.154	(0.22-1.07)	0.889	(0.16-5.08)	**0.107***	(0.02-0.61)
Other			Ref	Ref	Ref	Ref	Ref	Ref
Not Present = Reference								
Total Authorizations *(per company)*								
Core/Complementary Status								
Core EML	1.040	(0.96-1.13)	0.980	(0.92-1.04)	0.963	(0.90-1.03)	**0.896***	(0.82-0.99)
Complementary EML	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Medicine Size								
Biologic	1.056	(0.93-1.20)	1.051	(0.97-1.14)	**1.100***	(1.00-1.21)	1.086	(0.98-1.21)
Small Molecule	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Treatment Category								
Anti-infective medicines			1.030	(0.95-1.12)	1.022	(0.94-1.11)	**1.180***	(1.05-1.33)
Immunomodulators and antineoplastics			1.046	(0.96-1.14)	1.001	(0.93-1.08)	**1.233***	(1.07-1.42)
Other			Ref	Ref	Ref	Ref	Ref	Ref

***Significant Predictor**

Larger companies (determined by the number of marketing authorizations) held less core medicine authorizations in Uganda, although this effect was slightly diminished in a model accounting for all company-level factors (OR = 0.896; 95%CI = 0.82-0.99; OR = 0.879, 95%CI = 0.78-0.99). Large companies held more authorizations for biologic medicines than companies with less authorizations in Ecuador and Tunisia (OR = 1.080, 95%CI = 1.00-1.16; OR = 1.100, 95%CI = 1.00-1.21). These effects were exacerbated in a model including all predictors (OR = 1.195, 95%CI = 1.04-1.38; OR = 1.854, 95%CI = 1.11-3.11). Large companies were more likely to market anti-infectives and immunomodulators and antineoplastics in Uganda than smaller companies (OR = 1.180, 95%CI = 1.05-1.33; OR = 1.233, 95%CI = 1.07-1.42). Immunomodulators and antineoplastics were more likely to be marketed by larger companies in Uganda in a model including all company predictors (OR = 1.226, 95%CI = 1.03-1.43). In a

model with all company-level factors as predictors, larger companies were more likely to market biologic medicines in Brazil and Uganda (OR = 1.356, 95%CI = 1.09-1.68; OR = 1.313, 95%CI = 1.07-1.61).

Table 6b: Logistic Regression Model of All Company-Level Factors as Predictors of Core/Complementary Status, Medicine Size, and Treatment Category

	Latin America						Asia	
	Brazil (n = 59)		Colombia (n = 55)		Ecuador (n = 51)		Philippines (n = 52)	
Factors in the Model	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**
Company Presence								
Present								
Core/Complementary Status								
Core EML	0.995	(0.23-4.31)	1.183	(0.32-4.34)	1.184	(0.26-5.39)	**5.363***	(1.34-21.42)
Complementary EML	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Medicine Size								
Biologic	**0.001***	(0.00-0.17)	0.584	(0.11-3.02)	0.049	(0.00-1.22)	0.650	(0.14-3.08)
Small Molecule	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Treatment Category								
Anti-infective medicines	0.194	(0.03-1.47)	0.273	(0.05-1.48)	**0.021***	(0.00-0.40)	0.322	(0.06-1.71)
Immunomodulators and antineoplastics	0.306	(0.03-2.76)	0.712	(0.13-3.83)	0.079	(0.00-1.45)	0.908	(0.17-4.99)
Other	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Not Present = Reference								
Total Authorizations *(per company)*								
Core/Complementary Status								
Core EML	0.991	(0.93-1.05)	1.024	(0.96-1.10)	0.951	(0.88-1.02)	0.975	(0.91-1.05)
Complementary EML	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Medicine Size								
Biologic	**1.356***	(1.09-1.68)	1.055	(0.97-1.15)	**1.195***	(1.04-1.38)	1.038	(0.96-1.12)
Small Molecule	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Treatment Category								
Anti-infective medicines	0.942	(0.86-1.03)	1.020	(0.93-1.11)	0.891	(0.78-1.02)	0.963	(0.89-1.04)
Immunomodulators and antineoplastics	0.979	(0.89-1.08)	1.004	(0.92-1.10)	0.939	(0.83-1.07)	0.926	(0.84-1.02)
Other	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref

***Significant Predictor**

Table 6b: Logistic Regression Model of All Company-Level Factors as Predictors of Core/Complementary Status, Medicine Size, and Treatment Category

	Africa							
	South Africa (n = 19)		Tanzania (n = 48)		Tunisia (n = 42)		Uganda (n = 40)	
Factors in the Model	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**
Company Presence								
Present								
Core/Complementary Status								
Core EML	0.662	(0.07-6.23)	1.987	(0.37-10.64)	1.095	(0.16-7.74)	1.948	(0.19-20.14)
Complementary EML	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Medicine Size								
Biologic	1.061	(0.03-26.15)	0.281	(0.03-3.05)	**> 0.000***	(0.00-0.17)	**0.005***	(0.00-0.41)
Small Molecule	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Treatment Category								
Anti-infective medicines			0.138	(0.02-1.25)	0.876	(0.07-10.58)	0.506	(0.05-5.25)
Immunomodulators and antineoplastics			0.121	(0.01-1.44)	0.824	(0.08-8.84)	1.074	(0.06-18.53)
Other			Ref	Ref	Ref	Ref	Ref	Ref
Not Present = Reference								
Total Authorizations *(per company)*								
Core/Complementary Status								
Core EML	1.051	(0.95-1.16)	0.963	(0.89-1.04)	0.960	(0.88-1.05)	**0.879***	(0.78-0.99)
Complementary EML	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Medicine Size								
Biologic	1.054	(0.90-1.23)	1.084	(0.98-1.20)	**1.854***	(1.11-3.11)	**1.313***	(1.07-1.61)
Small Molecule	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Treatment Category								
Anti-infective medicines			0.968	(0.87-1.08)	1.017	(0.91-1.13)	1.150	(0.99-1.33)
Immunomodulators and antineoplastics			0.983	(0.88-1.10)	0.995	(0.89-1.11)	**1.226***	(1.03-1.45)
Other			Ref	Ref	Ref	Ref	Ref	Ref

***Significant Predictor**

Discussion

This study examined access to essential medicines in 8 LMICs using descriptive data, and analyzed the influence of medicine-, country-, and company-level factors using non-parametric correlation and logistic regression. Of the medicines included in our sample, LMICs had access to between 26%-84% of essential medicines centrally approved by the EU. This large discrepancy indicates the need for further research on the topic to better understand the challenges and barriers needed to overcome for equitable access to essential medicines in LMICs. This study observed factors related to the medicine, the company, and the target LMIC market that may influence the approval of medicines in LMICs and are described in further detail below. Key factors that are significantly related to the approval of medicines are core/complementary status, and treatment category, but only in Uganda and Tunisia.

Medicine-Level Factors

Only in Uganda and Tunisia did core/complementary status and treatment category significantly predict whether a medicine will be authorized in a LMIC. This means that core essential medicines were more likely to be approved in Uganda, whereas essential anti-infectives were less likely to be marketed in Tunisia. The bias in Uganda to authorize primarily core essential medicines may be attributed to their lower cost, as complementary medicines often entail additional costs (WHO, n.d.). This reflects the necessity for affordable medicines in lower-income countries as cost continues to pose an important barrier to medicine access (Cameron, 2009). The lower number of anti-infective medicine authorizations in Tunisia can be explained by the epidemiologic transition, and the recent focus on the prevalence of non-communicable diseases in the area (Romdhane et al., 2015, Khiari et al., 2021).

Country-Level Factors

Population size positively correlated with small molecule authorizations in LMICs for essential medicines centrally authorized in the EU. A larger population represents a larger potential market for medicines (Trim & Pan, 2005). There was a positive relationship between current HE per capita and the number of complementary, biologic, and immunomodulator and antineoplastic medicines, all of which are associated with higher costs (Ruff et al., 2016; Sangeetha et al., 2022). Higher HE is thus associated with access to more types of medicines, covering a larger range of treatment conditions. Furthermore, OOP HE was positively associated with the total number of medicine authorizations, as well as with many types of medicine authorizations. Prior studies have demonstrated that OOP HE were related to increased medicine

access for households in LMICs and HICs (Cherny et al., 2016; Hwang et al., 2001). However, OOP HE is also associated with food insecurity, financial insecurity, and disease comorbidity, suggesting that while populations may have access to more medicines, excessive OOP HE may have negative consequences for the population (Iragorri et al., 2021).

Disease burden per capita data would have offered more accurate results but was unfortunately not available online for the countries included in the study. Moreover, it would have been interesting to examine whether disease prevalence per country correlated with medicine access, however this information was also not available at the time. Furthermore, it is important to note that policies for government and regulatory agencies were not included but have been suggested to be barriers to medicine access in the past (Durán et al., 2021; Narsai & Mantel-Teeuwisse, 2012).

Company-Level Factors

Company presence was a significant predictor of core medicine authorizations in the Philippines, suggesting that companies which are present in the Philippines are more likely to market core medicines than companies which are not already present (Trim & Pan, 2005). Company size was also a significant predictor of medicine size and treatment category, although minimal when accounting for all company-level factors. These findings align with prior qualitative research where pharmaceutical companies reported more ease marketing medicines in countries where they had already established relationships with the government (Narsai & Mantel-Teeuwisse, 2012; Trim & Pan, 2005). However, results may have been skewed due to the approach for quantifying company presence used in this study.

The number of total authorizations held by a company was a significant predictor of core/complementary status, medicine size, and treatment category authorizations. Larger companies were more likely to market medicines associated with higher costs (i.e., complementary items, biologic medicines, and immunomodulators and antineoplastics) than smaller companies, especially when company presence was also included as a predictor. These findings align with the research (Brekke et al., 2014).

Strengths and Limitations

This study contains multiple strengths. Firstly, this research is the first to examine medicine-, country-, and company-level factors associated with essential medicine authorizations in LMICs, providing a more detailed insight into predictors of inequitable essential medicine access in LMICs. The use of the Bonair and Persson framework provides a basis upon which future research on the diffusion for medicines in LMICs may be conducted, leading to the creation of a more specific framework explaining access to essential medicines in LMICs. Secondly, the cross-sectional nature of the study highlights the current status of barriers impacting access to medicines across LMICs, thus indicating modern-day challenges to equitable medicine access in LMICs. Finally, this research was conducted in conjunction to a qualitative project providing further insight on the factors influencing companies to market medicines in LMICs. Together, both projects allow for a deeper understanding of challenges faced by pharmaceutical companies in marketing medicines in LMICs and the consequences of these challenges with regards to essential medicines.

As an explorative study, this research also has limitations. The study only explores one aspect of diffusion, adoption, as its cross-sectional nature cannot account for time. As such, no

causal conclusions can be drawn from the data. This is due to the lack of available information online regarding the dates of authorizations for essential medicines in LMICs. Furthermore, the study failed to explore access to essential medicines in additional countries due to the lack of online information in the languages of interest (although this study does integrate data from four UN languages: English, French, Portuguese, and Spanish). This resulted in a bias towards Latin American, and African countries. As such, no cross-continental comparisons could be drawn. Finally, data quantification and categorization posed an important challenge due to the nature of the data (e.g., company presence). These effects were hopefully minimized through the input of the advisory committee, which provided insight as how to best measure the variables of interest.

Future Implications

The results of this study highlight alarming discrepancies in the approval of essential medicines in the EU vs 8 LMICs and the different factors influencing it. These discrepancies are not only characteristic of the problem itself, as access to essential medicines is a multifaceted issue, but indicators of areas for improvement. Understanding predictors of access to medicines will lead to the creation of a better model for explaining this problem and improved policies to incentivize equitable access to medicines. More importantly, the barriers faced by this study suggest a critical need for more publicly available data to better understand this problem. With additional information on medicine authorizations across different countries, a more precise analysis can be conducted, while the date of first authorization for essential medicines can provide a better understanding of the full diffusion process of essential medicines. More specifically, further research may study delays in access to essential medicines in LMICs and explore the consequences of such delays, such as the economic burden this may place on national

healthcare systems. It should thus be a priority for LMICs, the WHO, and the World Bank to collect more information regarding actual and historical medicine authorizations, as well as information on medicine spending per country, to capture a more precise picture of factors influencing access to essential medicines in LMICs.

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Appendix 1

Table 7: Analyses Conducted and Variable Information

Analysis	Variable Name	Measurement	Variable Type
Logistic regression to determine whether medicine-level factors are predictors of local medicine authorizations in LMICs	Core/ complementary status	Binary coding (0 = complementary; 1 = core)	Binary and independent variable
	Medicine size	Binary coding (0 = small molecule; 1 = biologic)	Binary and independent variable
	Treatment category	Categorical coding (0 = other; 1 = immunomodulators and antineoplastics; 2 = anti-infectives)	Categorical and independent variable
	Authorizations	Binary coding (0 = not authorized; 1 = authorized)	Dependent
Kendall's tau non-parametric correlation to determine relationship between country-level factors and medicine authorizations	Population size	Current population size	Continuous
	Current health expenses per capita	Current health expenses per capita in USD	Continuous
	Out-of-pocket health expenses per capita	Out-of-pocket health expenses per capita in USD	Continuous
	Authorizations	Number of local medicine authorizations	Continuous
	Core/ complementary authorizations	Number of core/ complementary medicine authorizations	Continuous
	Medicine size	Number of small molecule/ biologic medicine authorizations	Continuous
	Treatment category	Number of anti-infective, immunomodulator and antineoplastics, and other authorizations	Continuous
Logistic regression to determine whether company-level factors are predictors of medicine authorization types in LMICs (according to medicine-level factors)	Company presence	Binary coding (0 = not present; 1 = present)*	Binary and independent variable
	Company size	Total number of essential medicine authorizations held by a company in our selection of LMICs	Continuous and independent variable
	Core/ complementary status	Binary coding (0 = complementary; 1 = core)	Binary and dependent variable
	Medicine size	Binary coding (0 = small molecule; 1 = biologic)	Binary and dependent variable
	Treatment category	Categorical coding (0 = other; 1 = immunomodulators and antineoplastics; 2 = anti-infectives)	Categorical and dependent variable

Appendix 2: Ethics Approval

P.O. Box 80140, 3508 TC Utrecht The Board of the Faculty of Social and Behavioural Sciences Utrecht University P.O. Box 80.140 3508 TC Utrecht		**Faculty of Social and Behavioural Sciences** Faculty Support Office Ethics Committee **Visiting Address** Padualaan 14 3584 CH Utrecht
Our Description	22-1160	
Telephone	030 253 46 33	
E-mail	FETC-fsw@uu.nl	
Date	06 April 2022	
Subject	Ethical approval	

ETHICAL APPROVAL

Study: Which Factors Influence Pharmaceutical Companies to Market New Essential Medicines to Low- and Middle-Income Countries? A quantitative analysis of 9 countries.

Principal investigator: M.T. Magdesian-De Skowronski

Supervisor: Katrina Perehudoff

The study is approved by the Ethical Review Board of the Faculty of Social and Behavioural Sciences of Utrecht University. The approval is based on the documents sent by the researchers as requested in the form of the Ethics committee and filed under number 22-1160. The approval is valid through 30 June 2022. The approval of the Ethical Review Board concerns ethical aspects, as well as data management and privacy issues (including the GDPR). It should be noticed that any changes in the research design oblige a renewed review by the Ethical Review Board.

Yours sincerely,

Peter van der Heijden, Ph.D.
Chair
This is an automatically generated document, therefore it is not signed

Appendix 3: SPSS Syntax

```
CROSSTABS
  /TABLES=BR SA EC CO TU TZ PH UG BY List CodCat MolBio
  /FORMAT=AVALUE TABLES
  /CELLS=COUNT
  /COUNT ROUND CELL.

ASSUMPTIONS: LOGIT LINEARITY (ALL MET)

    COMPUTE LnBRTA=LN(BRTA).
    COMPUTE LnCOTA=LN(COTA).
    COMPUTE LnECTA=LN(ECTA).
    COMPUTE LnPHTA=LN(PHTA).
    COMPUTE LnSATA=LN(SATA).
    COMPUTE LnTZTA=LN(TZTA).
    COMPUTE LnTUTA=LN(TUTA).
    COMPUTE LnUGTA=LN(UGTA).

    EXECUTE.

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LOGISTIC REGRESSION VARIABLES LIST
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LOGISTIC REGRESSION VARIABLES LIST
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LOGISTIC REGRESSION VARIABLES LIST
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LOGISTIC REGRESSION VARIABLES LIST
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LOGISTIC REGRESSION VARIABLES LIST
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  LOGISTIC REGRESSION VARIABLES LIST
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```

MULTICOLLINEARITY

```
  REGRESSION
    /MISSING LISTWISE
    /STATISTICS COEFF OUTS R ANOVA COLLIN TOL
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    /NOORIGIN
    /DEPENDENT LIST
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```

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LOGISTIC REGRESSION VARIABLES TU
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LOGISTIC REGRESSION VARIABLES EC
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LOGISTIC REGRESSION VARIABLES TU
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LOGISTIC REGRESSION VARIABLES TZ
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LOGISTIC REGRESSION VARIABLES PH
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LOGISTIC REGRESSION VARIABLES UG
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LOGISTIC REGRESSION VARIABLES CO
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LOGISTIC REGRESSION VARIABLES EC
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LOGISTIC REGRESSION VARIABLES TU
  /METHOD=ENTER CodCat
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```
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LOGISTIC REGRESSION VARIABLES BR
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LOGISTIC REGRESSION VARIABLES SA

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```

LOGISTIC REGRESSION VARIABLES CO

```
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```

```
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```
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DATASET ACTIVATE DataSet1.
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LOGISTIC REGRESSION VARIABLES MolBio
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  /CONTRAST (ECREACH)=Indicator(1)
  /PRINT=CI(95)
  /CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).

LOGISTIC REGRESSION VARIABLES MolBio
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```

```
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LOGISTIC REGRESSION VARIABLES List
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LOGISTIC REGRESSION VARIABLES List
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  /CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).

LOGISTIC REGRESSION VARIABLES MolBio
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  /CONTRAST (TZREACH)=Indicator(1)
  /PRINT=CI(95)
  /CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).

LOGISTIC REGRESSION VARIABLES List
```

```
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LOGISTIC REGRESSION VARIABLES MolBio
  /METHOD=ENTER UGREACH
  /CONTRAST (UGREACH)=Indicator(1)
  /PRINT=CI(95)
  /CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).

LOGISTIC REGRESSION VARIABLES MolBio
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LOGISTIC REGRESSION VARIABLES List
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LOGISTIC REGRESSION VARIABLES List
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  /PRINT=CI(95)
  /CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).

LOGISTIC REGRESSION VARIABLES List
  /METHOD=ENTER ECTA
  /PRINT=CI(95)
  /CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).

LOGISTIC REGRESSION VARIABLES List
  /METHOD=ENTER TUTA
  /PRINT=CI(95)
```

```
  /CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).

LOGISTIC REGRESSION VARIABLES List
  /METHOD=ENTER TZTA
  /PRINT=CI(95)
  /CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).

LOGISTIC REGRESSION VARIABLES List
  /METHOD=ENTER PHTA
  /PRINT=CI(95)
  /CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).

LOGISTIC REGRESSION VARIABLES List
  /METHOD=ENTER UGTA
  /PRINT=CI(95)
  /CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).


LOGISTIC REGRESSION VARIABLES MolBio
  /METHOD=ENTER BRTA
  /PRINT=CI(95)
  /CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).
```

```
LOGISTIC REGRESSION VARIABLES MolBio
  /METHOD=ENTER SATA
  /PRINT=CI(95)
  /CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).

LOGISTIC REGRESSION VARIABLES MolBio
  /METHOD=ENTER COTA
  /PRINT=CI(95)
  /CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).

LOGISTIC REGRESSION VARIABLES MolBio
  /METHOD=ENTER ECTA
  /PRINT=CI(95)
  /CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).

LOGISTIC REGRESSION VARIABLES MolBio
  /METHOD=ENTER TUTA
  /PRINT=CI(95)
  /CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).

LOGISTIC REGRESSION VARIABLES MolBio
  /METHOD=ENTER TZTA
  /PRINT=CI(95)
```

```
  /CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).

LOGISTIC REGRESSION VARIABLES MolBio
  /METHOD=ENTER PHTA
  /PRINT=CI(95)
  /CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).

LOGISTIC REGRESSION VARIABLES MolBio
  /METHOD=ENTER UGTA
  /PRINT=CI(95)
  /CRITERIA=PIN(0.05) POUT(0.10) ITERATE(20) CUT(0.5).

NOMREG CodCat (BASE=FIRST ORDER=ASCENDING) BY BRREACH
  /CRITERIA CIN(95) DELTA(0) MXITER(100) MXSTEP(5) CHKSEP(20) LCONVERGE(0)
PCONVERGE(0.000001)
    SINGULAR(0.00000001)
  /MODEL
  /STEPWISE=PIN(.05) POUT(0.1) MINEFFECT(0) RULE(SINGLE) ENTRYMETHOD(LR)
REMOVALMETHOD(LR)
  /INTERCEPT=INCLUDE
  /PRINT=PARAMETER SUMMARY LRT CPS STEP MFI.

NOMREG CodCat (BASE=FIRST ORDER=ASCENDING) BY SAREACH
```

```
  /CRITERIA CIN(95) DELTA(0) MXITER(100) MXSTEP(5) CHKSEP(20) LCONVERGE(0)
PCONVERGE(0.000001)
    SINGULAR(0.00000001)
  /MODEL
  /STEPWISE=PIN(.05) POUT(0.1) MINEFFECT(0) RULE(SINGLE) ENTRYMETHOD(LR)
REMOVALMETHOD(LR)
  /INTERCEPT=INCLUDE
  /PRINT=PARAMETER SUMMARY LRT CPS STEP MFI.

NOMREG CodCat (BASE=FIRST ORDER=ASCENDING) BY COREACH
  /CRITERIA CIN(95) DELTA(0) MXITER(100) MXSTEP(5) CHKSEP(20) LCONVERGE(0)
PCONVERGE(0.000001)
    SINGULAR(0.00000001)
  /MODEL
  /STEPWISE=PIN(.05) POUT(0.1) MINEFFECT(0) RULE(SINGLE) ENTRYMETHOD(LR)
REMOVALMETHOD(LR)
  /INTERCEPT=INCLUDE
  /PRINT=PARAMETER SUMMARY LRT CPS STEP MFI.

NOMREG CodCat (BASE=FIRST ORDER=ASCENDING) BY ECREACH
  /CRITERIA CIN(95) DELTA(0) MXITER(100) MXSTEP(5) CHKSEP(20) LCONVERGE(0)
PCONVERGE(0.000001)
    SINGULAR(0.00000001)
```

```
  /MODEL
  /STEPWISE=PIN(.05) POUT(0.1) MINEFFECT(0) RULE(SINGLE) ENTRYMETHOD(LR)
REMOVALMETHOD(LR)
  /INTERCEPT=INCLUDE
  /PRINT=PARAMETER SUMMARY LRT CPS STEP MFI.

NOMREG CodCat (BASE=FIRST ORDER=ASCENDING) BY TUREACH
  /CRITERIA CIN(95) DELTA(0) MXITER(100) MXSTEP(5) CHKSEP(20) LCONVERGE(0)
PCONVERGE(0.000001)
    SINGULAR(0.00000001)
  /MODEL
  /STEPWISE=PIN(.05) POUT(0.1) MINEFFECT(0) RULE(SINGLE) ENTRYMETHOD(LR)
REMOVALMETHOD(LR)
  /INTERCEPT=INCLUDE
  /PRINT=PARAMETER SUMMARY LRT CPS STEP MFI.

NOMREG CodCat (BASE=FIRST ORDER=ASCENDING) BY TZREACH
  /CRITERIA CIN(95) DELTA(0) MXITER(100) MXSTEP(5) CHKSEP(20) LCONVERGE(0)
PCONVERGE(0.000001)
    SINGULAR(0.00000001)
  /MODEL
  /STEPWISE=PIN(.05) POUT(0.1) MINEFFECT(0) RULE(SINGLE) ENTRYMETHOD(LR)
REMOVALMETHOD(LR)
```

```
  /INTERCEPT=INCLUDE
  /PRINT=PARAMETER SUMMARY LRT CPS STEP MFI.

NOMREG CodCat (BASE=FIRST ORDER=ASCENDING) BY PHREACH
  /CRITERIA CIN(95) DELTA(0) MXITER(100) MXSTEP(5) CHKSEP(20) LCONVERGE(0)
PCONVERGE(0.000001)
    SINGULAR(0.00000001)
  /MODEL
  /STEPWISE=PIN(.05) POUT(0.1) MINEFFECT(0) RULE(SINGLE) ENTRYMETHOD(LR)
REMOVALMETHOD(LR)
  /INTERCEPT=INCLUDE
  /PRINT=PARAMETER SUMMARY LRT CPS STEP MFI.

NOMREG CodCat (BASE=FIRST ORDER=ASCENDING) BY UGREACH
  /CRITERIA CIN(95) DELTA(0) MXITER(100) MXSTEP(5) CHKSEP(20) LCONVERGE(0)
PCONVERGE(0.000001)
    SINGULAR(0.00000001)
  /MODEL
  /STEPWISE=PIN(.05) POUT(0.1) MINEFFECT(0) RULE(SINGLE) ENTRYMETHOD(LR)
REMOVALMETHOD(LR)
  /INTERCEPT=INCLUDE
  /PRINT=PARAMETER SUMMARY LRT CPS STEP MFI.
```

```
NOMREG CodCat (BASE=FIRST ORDER=ASCENDING) BY BRREACH WITH BRTA
  /CRITERIA CIN(95) DELTA(0) MXITER(100) MXSTEP(5) CHKSEP(20) LCONVERGE(0)
PCONVERGE(0.000001)
    SINGULAR(0.00000001)
  /MODEL
  /STEPWISE=PIN(.05) POUT(0.1) MINEFFECT(0) RULE(SINGLE) ENTRYMETHOD(LR)
REMOVALMETHOD(LR)
  /INTERCEPT=INCLUDE
  /PRINT=PARAMETER SUMMARY LRT CPS STEP MFI.

NOMREG CodCat (BASE=FIRST ORDER=ASCENDING) BY ECREACH WITH ECTA
  /CRITERIA CIN(95) DELTA(0) MXITER(100) MXSTEP(5) CHKSEP(20) LCONVERGE(0)
PCONVERGE(0.000001)
    SINGULAR(0.00000001)
  /MODEL
  /STEPWISE=PIN(.05) POUT(0.1) MINEFFECT(0) RULE(SINGLE) ENTRYMETHOD(LR)
REMOVALMETHOD(LR)
  /INTERCEPT=INCLUDE
  /PRINT=PARAMETER SUMMARY LRT CPS STEP MFI.

NOMREG CodCat (BASE=FIRST ORDER=ASCENDING) BY COREACH WITH COTA
  /CRITERIA CIN(95) DELTA(0) MXITER(100) MXSTEP(5) CHKSEP(20) LCONVERGE(0)
PCONVERGE(0.000001)
```

```
    SINGULAR(0.00000001)
  /MODEL
  /STEPWISE=PIN(.05) POUT(0.1) MINEFFECT(0) RULE(SINGLE) ENTRYMETHOD(LR)
REMOVALMETHOD(LR)
  /INTERCEPT=INCLUDE
  /PRINT=PARAMETER SUMMARY LRT CPS STEP MFI.

NOMREG CodCat (BASE=FIRST ORDER=ASCENDING) BY TUREACH WITH TUTA
  /CRITERIA CIN(95) DELTA(0) MXITER(100) MXSTEP(5) CHKSEP(20) LCONVERGE(0)
PCONVERGE(0.000001)
    SINGULAR(0.00000001)
  /MODEL
  /STEPWISE=PIN(.05) POUT(0.1) MINEFFECT(0) RULE(SINGLE) ENTRYMETHOD(LR)
REMOVALMETHOD(LR)
  /INTERCEPT=INCLUDE
  /PRINT=PARAMETER SUMMARY LRT CPS STEP MFI.

NOMREG CodCat (BASE=FIRST ORDER=ASCENDING) BY TZREACH WITH TZTA
  /CRITERIA CIN(95) DELTA(0) MXITER(100) MXSTEP(5) CHKSEP(20) LCONVERGE(0)
PCONVERGE(0.000001)
    SINGULAR(0.00000001)
  /MODEL
```

```
  /STEPWISE=PIN(.05) POUT(0.1) MINEFFECT(0) RULE(SINGLE) ENTRYMETHOD(LR)
REMOVALMETHOD(LR)
  /INTERCEPT=INCLUDE
  /PRINT=PARAMETER SUMMARY LRT CPS STEP MFI.

NOMREG CodCat (BASE=FIRST ORDER=ASCENDING) BY PHREACH WITH PHTA
  /CRITERIA CIN(95) DELTA(0) MXITER(100) MXSTEP(5) CHKSEP(20) LCONVERGE(0)
PCONVERGE(0.000001)
    SINGULAR(0.00000001)
  /MODEL
  /STEPWISE=PIN(.05) POUT(0.1) MINEFFECT(0) RULE(SINGLE) ENTRYMETHOD(LR)
REMOVALMETHOD(LR)
  /INTERCEPT=INCLUDE
  /PRINT=PARAMETER SUMMARY LRT CPS STEP MFI.

NOMREG CodCat (BASE=FIRST ORDER=ASCENDING) BY UGREACH WITH UGTA
  /CRITERIA CIN(95) DELTA(0) MXITER(100) MXSTEP(5) CHKSEP(20) LCONVERGE(0)
PCONVERGE(0.000001)
    SINGULAR(0.00000001)
  /MODEL
  /STEPWISE=PIN(.05) POUT(0.1) MINEFFECT(0) RULE(SINGLE) ENTRYMETHOD(LR)
REMOVALMETHOD(LR)
  /INTERCEPT=INCLUDE
```

```
  /PRINT=PARAMETER SUMMARY LRT CPS STEP MFI.
```