

Comparing the cost of medicines across countries is of great importance for global health decision-makers. A method for comparing cost and for assessing the determinants of its variability is warranted.

Comparing the Price of Medicines at a Global Level. The Experience of an Italian WHO Collaborating Centre.

Elisabetta Pasi¹, Roberta Giroladini¹, Francesco Nonino¹, Thomas Piggott², Holger J Schunemann^{2,3}, Deanna Saylor⁴, Nick Rijke⁵, Joanna Laurson-Doube⁵, Elisa Sangiorgi¹

BACKGROUND

- When developing drug treatment recommendations, several important decisional criteria should be considered, ensuring that the best available research evidence informs them.
- Cost is a key component, particularly from a population perspective, since it will affect how resources will be used.
- In limited resource settings (e.g. low- and middle income countries), cost may be one of the factors driving recommendations, substantially impacting their feasibility and acceptability by the key stakeholders
- The GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) Evidence to Decision (EtD) frameworks integrate, among others, cost and resource utilization assessment [1].
- Assessing drug prices, often the main component of treatment cost, is challenging due to multiple determinants of variability.
- Methods for systematically assessing and comparing cost of medicines are lacking
- In 2021 and 2022 the Multiple Sclerosis International Federation (MSIF) appointed two multi-stakeholder guideline development groups to develop evidence-based recommendations on disease-modifying treatments for multiple sclerosis (DMTs) from a limited resource setting perspective by means of the GRADE methodology
- By adopting the EtD framework, cost and resource use of different available DMTs were assessed
- The WHO Collaborating Centre in Evidence-Based Research Synthesis and Guideline Development, Bologna, Italy, performed a cost comparison at a global level to assess differences in prices of DMTs across countries
- The WHO Collaborating Centre co-developed with MSIF an application, informed by the recommendations of the guideline development groups, for the inclusion of DMTs in the 23rd WHO Essential Medicines List (EML) with the aim of improving treatment access worldwide.
- Cost assessment is recommended by the WHO when applying for the inclusion of medicines in the EML.

METHODS

Search, selection, data extraction

- Manual search of publicly available databases (non-commercial governmental agencies, HTA reports and expert input).
- Sample of countries, by income level (World Bank Classification), selected by the public availability of drug prices.
- Ex-factory (ex-work) price extracted whenever available (recommended by the WHO) [2]. Cheapest available alternative considered.
- Extraction of unit price (i.e., price for one TAB, one CAP, one Vial, etc.) for each available dosage.

Comparability

- Cost/patient/year computed by multiplying the cost of a drug unit by the number of yearly administrations according to the dose schedule reported by the Summary of Product Characteristics labelling information. In case of individualized dosage (e.g. mg / Kg, or /unit of body surface) or when used off-label, dose averaging from pivotal RCTs or from expert input.
- Local currencies converted into US Dollars (currency exchange rate updated on June 6, 2022 via <https://www.xe.com/>).
- All terms are compliant with the Glossary of the 2022 Vienna WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies Glossary of pharmaceutical terms [3].

RESULTS

- Prices of 25 labelled and off-label DMTs, branded and unbranded, were included from 18 countries (3 HIC, 7 UMIC, 8 LMIC) (Table 1).
- The multi-stakeholder panels appointed by MSIF, selected three DMTs for inclusion in the 23rd WHO EML: **rituximab** (in square box grouping with ocrelizumab), **cladribine** and **glatiramer acetate**. (Table 2, Table 3)
- Price comparison was reported in detailed tables for all 25 DMTs considered (an example of reporting is provided in Table 4)
- No price information available from LICs

CONCLUSIONS

- Prices of DMTs for multiple sclerosis vary substantially across countries
- No information on prices of DMTs for multiple sclerosis is available from low income countries
- Developing a method for systematically comparing drug prices is of great importance for informing health decisions from a population perspective, such as that of the WHO EML Expert Committee.
- Systematic drug price comparison may improve the quality of applications for the inclusion of medicines in the WHO EML and inform health decision-makers when addressing affordability.
- Investigating the determinants of the variability of drug prices across countries is warranted.

TABLE 1 - Countries providing cost information on DMTs included in the comparison

Country	Income level*
Italy, Norway, US (VA)	HIC (High Income Country)
Brazil, Colombia, Lebanon, Malaysia, Serbia, South Africa, Turkey	UMIC (Upper-Middle Income Country)
Ghana, India, Iran, Kenya, Morocco, Nigeria, Sri Lanka, [LMIC-confidential]	LMIC (Low- Middle Income Country)

* World Bank classification; VA= Veterans Affairs

TABLE 2 - DMTs proposed for inclusion in the 23rd WHO EML

Medicine	ATC code	Dosage, Form, Strength	Registered indications (EMA)
Rituximab	L01FA01	10 mg per mL in 50 mL vial, concentrate for solution for infusion (intravenous route)	Off label
therapeutic alternatives**: ocrelizumab	L04AA36	30 mg per mL in 10 mL vial, concentrate for solution for infusion (intravenous route)	Treatment of adult patients with relapsing MS with active disease and early primary progressive MS.
Cladribine (oral formulation)	L04AA40	10 mg tablets (oral route)	Treatment of adult patients with highly active relapsing MS.
Glatiramer acetate	L03AX13	20 mg per mL or 40 mg per mL, solution for injection (subcutaneous route)	Treatment of relapsing MS; glatiramer acetate is not indicated in primary or secondary progressive MS. [§]

** Including quality-assured biosimilars; † Licensed through national procedure; EMA= European Medicines Agency

TABLE 3 - DMTs proposed for inclusion in the 23rd WHO EML: median price (cost/patient/year, USD) and price range

Drug, formulation	HIC [range]	UMIC [range]	LMIC [range]
Cladribine (Mavenclad®) 10mg TAB	26,298 [24,684 – 62,628]	23,834 [9,480-31,104]	6,602 * (LMIC#)
Glatiramer acetate 40 mg/ml INJ	8,511 [6,355 -12,566]	6,618 [1,987 – 11,797]	960 * (Iran)
Ocrelizumab (Ocrevus®) 300 mg/10 ml INJ	24,192 [24,090 - 66,681]	17,928 [6,790 - 25,296]	4,600 [1,200 – 22,580]
Rituximab 500 mg, 10 mg/ml INJ **	4,298 [3,912 – 8,813]	3,089 [2,899 – 4,596]	2,330 [120 – 7,184]

HIC=high income countries, INJ=injectable, LMIC= lower-middle income countries, TAB=tablets, UMIC=upper-middle income countries; * Only one value available; ** for RRMS and PMS; § Mean (two values available); # country asking to remain confidential. Currency exchange rates as of June 6, 2022

TABLE 4 - EXAMPLE OF REPORTING TABLE

Prices of disease modifying treatments for RMS in a sample of Low-Middle income countries (LMIC)

Prices are ex-factory, unless otherwise indicated and do not include VAT and duties/fees for distribution by the pharmacies

Currency: USD

Exchange rates: www.xe.com [accessed 06/06/2022 unless otherwise specified]. 1 INR = 0,0128775 USD, 1 USD = 77,6547 INR; 1 NGN = 0,00240890 USD, 1 USD = 415,127 NGN; 1 GHS = 0,126659 USD, 1 USD = 7,89519 GHS; 1 KES = 0,00854762 USD, USD = 116,992 KES

Prices in green=lowest price among considered LMICs; Prices in red=highest price among considered LMICs

Drug, formulation	Nigeria†				Ghana†				Morocco†				India**			
	NPP	NPP CPY	BUP	BUP CPY	NPP	NPP CPY	BUP	BUP CPY	NPP	NPP CPY	BUP	BUP CPY	NPP	NPP CPY	BUP	BUP CPY
Ocrelizumab (Ocrevus®) 300 mg/10 ml INJ	-	-	-	-	-	-	876	3,504	-	-	5,645	22,580	-	-	-	-
Rituximab 500 mg, 10 mg/ml INJ	394.59	1,578	-	-	-	-	-	-	-	-	1,215	4,860	141.68	566.72	-	-

Drug, formulation	Sri Lanka †				[LMIC]† **				Kenya †				Iran †			
	NPP	NPP CPY	BUP	BUP CPY	NPP	NPP CPY	BUP	BUP CPY	NPP	NPP CPY	BUP	BUP CPY	NPP	NPP CPY	BUP	BUP CPY
Cladribine (Mavenclad®) 10mg TAB	-	-	-	-	-	-	NA	6,602	-	-	-	-	-	-	-	-
Glatiramer acetate 40 mg/ml INJ	-	-	-	-	-	-	-	-	-	-	-	-	-	-	NA	960
Ocrelizumab (Ocrevus®) 300 mg/10 ml INJ	-	-	-	-	-	-	1,423	5,693	-	-	-	-	NA	1,200	-	-
Rituximab 500 mg, 10 mg/ml INJ	-	-	-	-	-	-	582	2,329	1,026	4,104	1,796	7,184	NA	120	-	-

* Expert input (personal communication); ** Negotiated price; † Confidential expert input from LMIC; ‡ Expert input (personal communication). Wholesale price; * India <https://www.nppaindia.nic.in/wp-content/uploads/2020/10/Ceiling-Price-List-F.pdf> (accessed 31.03.2022); † Expert input (personal communication).

ABBREVIATIONS

BUP=Brand Unit Price; CPY=cost per-patient-per-year; INJ=injectable; NA=Not available; NPP=Non-Proprietary Name Unit Price; POW=powder for injection; TAB=tablet.

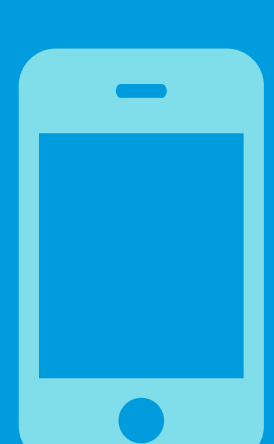
ASSUMED DOSAGE

- Cladribine: 10 mg TAB/day for two weeks (2 one week cycles)= 12 x 10 mg TABs (weight range from 60 to 70kg)
- Glatiramer acetate: 1 x 40mg vial x3/week s.c. = 156 x 40 mg vials per year
- Rituximab: 6 x 500mg vials per year (starting dose 1,000mg i.v. twice two weeks apart, retreatment 1,000mg after 6-9 months);
- Ocrelizumab: 1 x 600mg vial /6 months i.v. = 4 x 300mg vials per year

REFERENCES

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¹ WHO Collaborating Centre in Evidence-Based Research Synthesis and Guideline Development. Assessorato politiche per la salute. Direzione Generale Cura della Persona, Salute e Welfare. Area Governo del Farmaco e dei Dispositivi Medici - Settore Assistenza Ospedaliera, Bologna, Italy, ² Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Canada; ³ Department of Biomedical Sciences, Humanitas University, Milan, Italy; Michael G. DeGroot Cochrane Canada Centre & McMaster GRADE Centre, McMaster University, Hamilton, ON, Canada; ⁴ Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD USA; ⁵ Multiple Sclerosis International Federation, London, UK



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