



Paving the way for affordable and equitable liposomal amphotericin B access worldwide

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Amphotericin B has long been crucial for treating many serious infectious diseases, such as invasive fungal infections and visceral leishmaniasis, particularly for patients who are immunocompromised, including those with advanced HIV infection. The conventional amphotericin B deoxycholate formulation has largely been replaced in high-income countries with liposomal amphotericin B (LAmB), which has many advantages, including lower rates of adverse events, such as nephrotoxicity and anaemia. Despite an evident need for LAmB in low-income and middle-income countries, where mortality from invasive fungal infections is still substantial, many low-income and middle-income countries still often use the amphotericin B deoxycholate formulation because of a small number of generic formulations and the high price of the originator LAmB. The pricing of LAmB is also highly variable between countries. Overcoming supply barriers through the availability of additional quality-assured, generic formulations of LAmB at accessible prices would substantially facilitate equitable access and have a substantial effect on mortality attributable to deadly fungal infections.

Introduction

Fungal infections are becoming an increasing problem worldwide. This problem is highlighted by WHO publishing their first ever list of fungal priority pathogens in 2022.¹ It is clear that effective treatment of these fungal infections is crucial. However, in countries with low infrastructure and workforce resources, which often have high rates of fungal infections, access to appropriate drugs can be challenging. In this Health Policy, we present our view of the situation relating to amphotericin B. The broad-spectrum antifungal, amphotericin B, was discovered in 1953, when it was isolated from the bacterium *Streptomyces nodosus*.² To this day, it remains one of the most important drugs for treating invasive fungal infections and is a key component of the treatment for the parasitic infection leishmaniasis.^{3,4} However, the conventional amphotericin B deoxycholate formulation is also substantially toxic to mammalian cells; associated clinical toxicities often necessitate treatment modification or discontinuation,⁵ so its use requires careful monitoring.² Nephrotoxicity is of particular concern, and haematological toxicity can lead to normochromic, normocytic anaemia.⁶ In addition, this formulation requires a long administration period (2–6 h) via intravenous infusion, protection from light, and complex handling to ensure adequate dilution, which restricts its use to hospital settings, especially in low-income and middle-income countries (LMICs).⁶

The development of liposomal amphotericin B (LAmB), a lipid-based formulation, has provided a drug with a much more favourable tolerability and toxicity profile than the amphotericin B deoxycholate formulation.^{7,8} Importantly, LAmB has a clinically significantly lower nephrotoxicity risk than the amphotericin B deoxycholate formulation⁹ and has, therefore, been a preferred choice since it became

available in 1993, including in combination therapy with agents such as fluconazole and flucytosine for the treatment of cryptococcal meningitis.¹⁰ LAmB has a broad spectrum of activity, similar to the amphotericin B deoxycholate formulation, and is thus currently used for a wide range of potentially fatal invasive fungal infections; it is used as an empirical therapy for presumed fungal infection in patients who are febrile with neutropenia; for the treatment of histoplasmosis, cryptococcal meningitis, and talaromycosis for people living with HIV; for the treatment of invasive aspergillosis, candidiasis, and cryptococcal disease (including for patients refractory to amphotericin B deoxycholate formulation or in those for whom renal impairment or unacceptable toxicity precludes the use of amphotericin B deoxycholate formulation); and for the treatment of visceral leishmaniasis.^{11–13} It is recommended by WHO as the preferred treatment for cryptococcal meningitis, visceral leishmaniasis, and histoplasmosis.^{14–16}

In some clinical situations, such as patients with cancer who have neutropenia, LAmB might be more effective at controlling invasive fungal infections than amphotericin B deoxycholate formulation, as well as having a better toxicity profile.¹⁷ There is also evidence to suggest that LAmB can be effective as an intermittent or single dose in many situations, shortening the time needed for hospital administration.¹⁸ For example, for cryptococcal meningitis, a single high dose of LAmB was shown to be non-inferior to 7 days' treatment with amphotericin B deoxycholate formulation,¹⁹ and is now recommended as the standard of care by WHO and the European Confederation of Medical Mycology and International Society for Human and Animal Mycology guidelines.^{14,20} A proof of concept study found a single infusion of LAmB for patients with visceral leishmaniasis was non-inferior to, and was less expensive than, amphotericin B

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deoxycholate formulation administered every other day over 29 days.²¹ A phase 2 study in histoplasmosis shows similar results,²² and phase 3 studies are being planned. These characteristics suggest a compelling case for displacing the conventional formulation with LAmB in these settings.

Despite the clear advantages of LAmB, the conventional amphotericin B deoxycholate formulation is still often used in clinical practice, primarily for financial reasons.²³ In addition to LAmB, other formulations of amphotericin B have been developed, including a colloidal dispersion and a lipid complex, with similar efficacy but clinically significant safety benefits associated with the lipid products.²⁴ The amphotericin B colloidal dispersion, which is no longer commercially available, had an equivalent or increased frequency of infusion-related reactions compared with the amphotericin B deoxycholate formulation.²⁴ The amphotericin B lipid complex formulation is less nephrotoxic than the amphotericin B deoxycholate formulation, but more nephrotoxic than LAmB.²⁵ There is a scarcity of substantive evidence on non-inferiority

or superiority of amphotericin B lipid complex versus LAmB, with LAmB having better efficacy than amphotericin B lipid complex in some situations, in particular for treating brain and other difficult-to-treat infections.²⁵ For these reasons, LAmB currently remains the preferred formulation.

A 2016 report highlighted that access to any form of amphotericin B was only available in 42 of 155 countries and that, where it was available, pricing varied widely.²⁶ WHO defines health equity as “the absence of unfair, avoidable or remediable differences in health among groups of people”.²⁷ This variability in availability and pricing highlights the need for equitable access to liposomal amphotericin B across LMICs. The aim of this Health Policy is to provide information on the pricing of, and demand for, amphotericin B injectable formulations worldwide, and to give examples of estimated demand for LAmB in two middle-income countries (MICs), Brazil and Malaysia. These countries were chosen because they highlight different reasons for inequitable access to LAmB in relation to availability and pricing (panel). This information builds a

Panel: Middle-income country LAmB access examples

These examples of two very different situations in middle-income countries (Brazil and Malaysia) highlight issues with access to liposomal amphotericin B (LAmB), which vary from country to country.

Previous research has shown a particular burden of candidiasis and aspergillosis in Malaysia, whereas cryptococcosis is a burden in people living with HIV in Malaysia and accounts for around 2–8 cases per 100 000 population; amphotericin B injection is indicated for either first-line or alternative treatments for these systemic fungal infections, among others.²⁸ In Malaysia, LAmB is needed as an alternative to amphotericin B deoxycholate for treatment of systemic fungal infections such as aspergillosis, cryptococcal meningitis, histoplasmosis, and penicilliosis. In situations in which a higher dose of amphotericin B would be needed, such as for mucormycosis, LAmB is the preferred treatment choice. In 2021, in the public sector, 29 457 vials of amphotericin B deoxycholate were purchased for use at the price of MYR 39 (equivalent to US\$8) and 1186 vials of amphotericin lipid complex were purchased for use at the price of MYR 432 per vial (\$91). During this period, only 28 vials of LAmB injections were purchased at the same price as the amphotericin lipid complex. Price is the main barrier for accessing a better amphotericin B formulation in Malaysia. Considering the greater efficacy and lower toxicity of LAmB, the combined sales volumes of amphotericin B deoxycholate and amphotericin lipid complex in Malaysia could be replaced with LAmB if the price were affordable.

Brazil was able to purchase 120 000 vials of LAmB for visceral leishmaniasis from Gilead Sciences in 2022 at the no-profit price of US\$16.25 per vial. Due to the excessively high price of LAmB

when compared with the no-profit price (over \$200 per vial, for diseases other than visceral leishmaniasis), it is not, however, widely available for indications other than visceral leishmaniasis because Brazil does not benefit from the no-profit price for cryptococcal meningitis or other infections. Fungal infections are not notifiable infections in Brazil, so the precise rates and burden of these diseases can be difficult to establish. In Brazil, cryptococcosis—one of the most lethal fungal infections among people living with HIV—is one of the main intended uses for amphotericin B injection.²⁹ Latin America has the third largest number of cases of cryptococcal meningitis in the world, after sub-Saharan Africa and the Asia-Pacific regions, respectively; and Brazil has the highest rates within Latin America, at around 1001–2500 new cases a year.³⁰ Other important indications for LAmB use include histoplasmosis, with an estimated mortality rate of 33% in Brazil, and candidiasis, which also has high morbidity and mortality rates.^{31,32} Amphotericin B is also an alternative treatment option for coccidioidomycosis, which is endemic in northeastern Brazil.³³ In 2022, in Brazil’s public sector, 47 982 vials of amphotericin B deoxycholate were purchased for use at the price of \$4.75 per vial, 119 400 vials of amphotericin lipid complex were purchased for use at the price of \$24–105 per vial, and 117 270 vials of LAmB were purchased for use at the price of \$215 per vial. The current sales volumes of amphotericin B deoxycholate and amphotericin lipid complex could be replaced by the more efficacious and less toxic LAmB if an affordable LAmB product was available in Brazil. These two examples show that there is a potential demand for LAmB in low-income and middle-income countries with a large market size.

convincing case for the need to improve provision of LAmB in LMICs.

The need for amphotericin B in the treatment of infectious diseases

Some researchers suggest that, of patients with life-threatening fungal infections, an estimated 80% could be saved if they could access current diagnostics and treatments.³⁴ Although this estimate might be considered optimistic, access to amphotericin B is crucial, including for the top ranked Critical group of fungal pathogens by WHO (*Cryptococcus neoformans*, *Candida auris*, *Aspergillus fumigatus*, and *Candida albicans*) that can mostly be treated with amphotericin B.¹ The disease burden of invasive fungal infections varies widely across the world and is largely driven by the HIV/AIDS epidemic, tuberculosis, chronic obstructive pulmonary disease, asthma, and cancer.³⁴ High-income countries (HICs) with effective control measures for these diseases tend to have lower rates of fungal infections than LMICs;^{35–38} however, invasive candidiasis and candidemia remain major considerations in HICs for people who are immunocompromised as a result of chemotherapy and transplantation.³⁹ In LMICs, there is a complex pattern of invasive fungal epidemiology, particularly in relation to HIV prevalence.³⁹ It is estimated that the case-fatality rate of cryptococcal meningitis is 15–20% in the USA, but greater than 50% in LMICs.⁴⁰ Similarly, mortality due to histoplasmosis reaches 25% in people living with HIV.⁴¹ There is emerging evidence that the epidemiology of a number of important invasive fungal infections is changing due to climate change.⁴² The recent mucormycosis crisis in India, during the second wave of COVID-19 in 2021, augmented the demand for amphotericin B, which triggered the Indian Government to build national supply and restrict export.⁴³

Although there is a greater need for amphotericin B in LMICs than HICs, LAmB has an added value because many LMICs have limited capacity to monitor and manage toxicities, which occur more often with amphotericin B deoxycholate formulation than LAmB. It is also important to consider the severe functional impairment that can occur in people with cryptococcal disease, even after treatment,⁴⁴ so avoiding further medical complications from treatment is key. Shorter treatment times, with shorter hospitalisation and monitoring, which are becoming possible with the development of single high-dose LAmB therapies for cryptococcal meningitis, visceral leishmaniasis, and histoplasmosis, will also be of benefit for LMICs.^{19,21,22}

Currently available formulations of amphotericin B

There are three different formulations of amphotericin B currently available for use worldwide. Conventional amphotericin B is a deoxycholate formulation, which allows the generally insoluble drug to form micelles in

aqueous solution.⁴⁵ Amphotericin B lipid complex is made by combining dimyristoyl phosphatidylcholine and dimyristoyl phosphatidylglycerol with amphotericin B, which forms a concentration of ribbon-like structures of a bilayered membrane.⁴⁶ LAmB consists of a stable ionic complex with a lipid bilayer in the form of small unilamellar vesicles made up of hydrogenated soy phosphatidylcholine and distearoylphosphatidylglycerol stabilised with cholesterol.⁴⁶ Surveys from the European Confederation of Medical Mycology and International Society for Human and Animal Mycology in Asia and Africa suggest that amphotericin B is available in an estimated 188 (80·0%) of 235 clinics that responded in Asia, with 144 (61·3%) having access to the amphotericin B deoxycholate formulation, 67 (28·5%) to amphotericin B lipid complex, and 135 (57·4%) to LAmB; whereas in Africa, 21 (52·5%) of 40 clinics that responded had access to amphotericin B deoxycholate formulation, 4 (10·0%) to amphotericin B lipid complex, and 7 (17·5%) to LAmB.^{47,48}

There are generic forms of LAmB available, but its complex chemical structure makes it difficult to manufacture; other manufacturers have previously tried and failed to produce LAmB.⁴⁹ Manufacturing processes that produce different sized liposome structures can result in faster drug release and increased drug toxicity.⁴⁹ Therefore, straightforward regulatory guidance for producers of LAmB is particularly important, and clear guidelines on bioequivalence, evaluation, and dose have been issued by the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and WHO pre-qualification. Today, the technical barriers to the availability of alternative LAmB products have largely been addressed.⁵⁰ Although generic liposomal amphotericin B products have been available in some countries for several years, it is assumed that the majority of these products would be unable to show equivalence to AmBisome (Gilead Sciences, Foster City, CA, USA)—an originator registered LAmB product—in accordance with FDA and EMA requirements. Nevertheless, there are two generic products (from Sun Pharma and Eugia Pharma Specialties) that have received FDA approval and one (from Tillomed Laboratories) that has been approved by the UK Medicines Healthcare products Regulatory Agency^{51–54} of 19 generic LAmB manufacturers, which severely limits access to generic LAmB for LMICs that suffer a disproportionate burden of infections that require this drug for treatment.

Price and demand analysis

To understand the global market for the three currently available amphotericin B injectable formulations (amphotericin B deoxycholate formulation, LAmB, and amphotericin B lipid complex) we first analysed monthly sales values and volumes data for 53 countries from 2017 to 2021, provided under licence by IQVIA from the IQVIA MIDAS information service.⁵⁵ IQVIA MIDAS provides

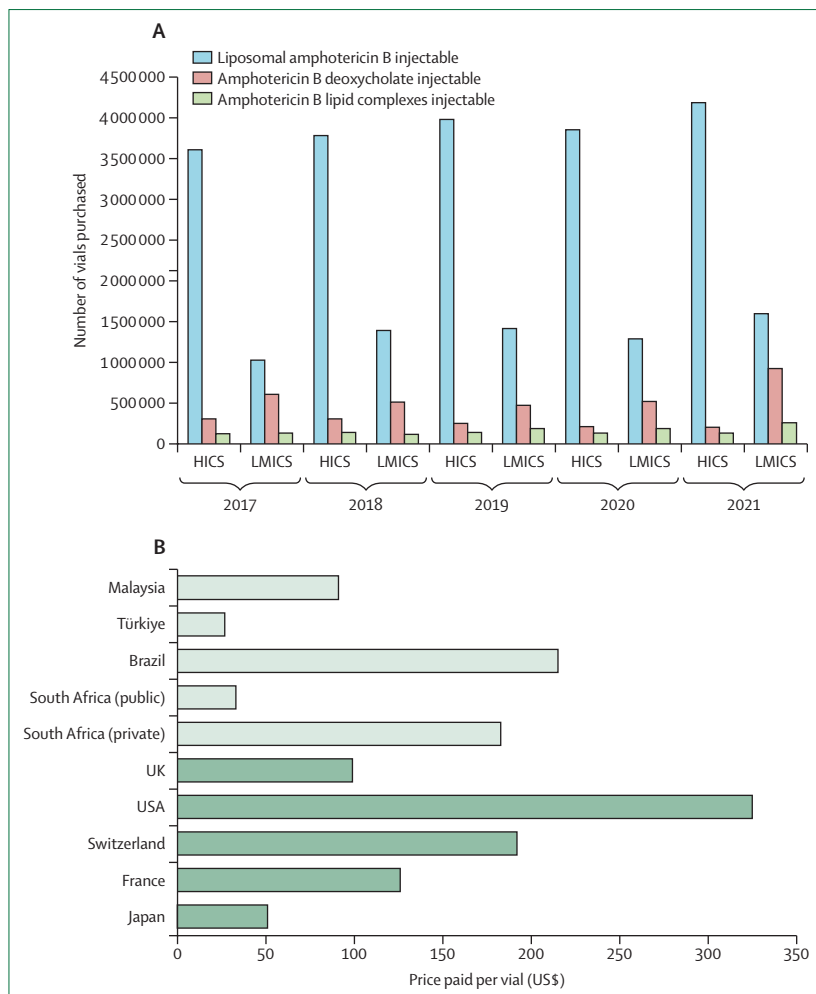


Figure: Price and demand analysis
 (A) Quantities of the three different amphotericin B formulations purchased between 2017 and 2021 in HICs and LMICs. Our analysis is based on IQVIA MIDAS data of monthly volume sales for January, 2017, to December, 2021, reflecting estimates of real-world activity.⁵⁵ (B) Price of liposomal amphotericin B (AmBisome) in selected high-income (red) and middle-income (blue) countries. The price of AmBisome was obtained from the Pharmaceutical Services Programme of the Ministry of Health (Malaysia), Kyoto Encyclopedia of Genes and Genomes (Japan), ViDAL.fr (France), HCl Compendium (Switzerland), Drugs.com (USA), British National Formulary (UK), Medicine Price Registry (South Africa), Ministry of Health (Brazil), and RxMediaPharma (Türkiye). Prices are shown in US\$, converted from the local currency at exchange rates of November, 2023. Liposomal amphotericin B is not registered in Malaysia; the price stated relates to an import with special approval from the Malaysian Ministry of Health. HICs=high-income countries. LMICs=low-income and middle-income countries.

volume and by sales value compared with the amphotericin B deoxycholate formulation and amphotericin B lipid complex. The market for LAmB is mainly dominated by AmBisome, and the generic market captures approximately 4% of the total sales value. In 2021, 4.18 million vials (72%) of LAmB were sold in HICs compared with 1.60 million vials (28%) in LMICs (figure). However, LMICs purchased more amphotericin B deoxycholate formulation (927 963 vials; 82%) and amphotericin B lipid complex (262 636 vials; 67%) than HICs (206 659 vials [18%] of amphotericin B deoxycholate formulation and 131 861 vials [33%] of amphotericin B lipid complex). In 2021, 5.8 million LAmB vials were sold, totalling US\$510 million, compared with 1.1 million amphotericin B deoxycholate formulation injections, totalling \$17 million, and 394 000 amphotericin B lipid complex injections, totalling \$24 million.

The price of LAmB was generally considerably higher than both the amphotericin B deoxycholate formulation and amphotericin B lipid complex. Our analysis of the AmBisome price shows it is inconsistently priced worldwide (figure), which disregards the need for the drug and does not correlate with the ability of countries or communities to pay. This inconsistent pricing is similar to the findings of a previous study that highlighted the price disparity of a 50 mg vial of LAmB compared with the gross national income of a country.⁵⁷ LMICs with a high burden of HIV, including Brazil, Peru, South Africa, and Thailand, paid far more for AmBisome than European HICs such as Belgium, France, Luxembourg, Spain, and Switzerland.⁵⁷ In MICs, AmBisome can be found at \$27 per vial in Türkiye, but \$215 per vial in Brazil—a higher price than is paid by HICs such as Japan (\$51), France (\$126), the UK (\$99), and Switzerland (\$192). Such high prices deter countries from prioritising access to LAmB, which is of concern because LAmB should replace the amphotericin B deoxycholate formulation and amphotericin B lipid complex, as has largely taken place in HICs, due to its superior efficacy, reduced toxicity, and ease of use.

There have been some attempts at providing low-price LAmB to LMICs. Gilead Sciences recently extended an agreement, signed with WHO in 2011, to provide AmBisome through a donation programme for 11 countries.⁵⁸ Another approach is the provision of a down-negotiated price. This reduced price has been an option for visceral leishmaniasis and cryptococcal meningitis in some situations in which AmBisome has been offered by Gilead Sciences at \$16.25 per vial to the public sector and to not-for-profit organisations.⁵⁹ Access to Gilead Sciences' no-profit price has been challenging, with long lead times, supply shortages, and cumbersome reporting (intended to prevent product diversion to other indications). Therefore, Gilead Sciences' no-profit price is only offered to 116 LMICs for specific indications, and the countries still have access challenges, such as

For more on the **Malaysian Pharmaceutical Services Programme** see <https://pharmacy.moh.gov.my/en>
 For more on the **Kyoto Encyclopedia of Genes and Genomes** see <https://www.kegg.jp/>
 For more on **ViDAL.fr** see <https://www.vidal.fr/>
 For more on the **HCl Compendium** see <https://compendium.ch/>
 For more on **Drugs.com** see <https://www.drugs.com/>

estimated product volumes of registered medicines, trends, and market share through retail and non-retail channels. In addition to this service, we obtained data directly from the ministries of health of both Brazil and Malaysia. We also researched prices cited by public and non-public sources. The coverage of market data varies for each country in the IQVIA MIDAS database, and in HICs the data coverage is 85–100%. For these analyses, we used the World Bank country classification of HICs, MICs, and low-income countries based on gross national income per capita, calculated using the World Bank Atlas.⁵⁶

Analysis of the IQVIA MIDAS data from 2017 to 2021 showed that LAmB has the biggest market share by

availability of stock for order fulfilment, product not registered, or unavailability of the product due to exclusive marketing agreements.⁵⁷ Although Gilead Sciences' no-profit price might enable access in some areas, it has not yet been proven to be a viable solution for sustainable and widespread LAmB access in LMICs. Furthermore, in 2023, Gilead Sciences announced that, as of Jan 1, 2024, its no-profit price offer would increase by 40%, from \$16·25 to \$23 per vial.⁶⁰

A number of important indications in LMICs, including leishmaniasis, cryptococcal meningitis, histoplasmosis, and mucormycosis, still require a safer and more efficacious treatment than amphotericin B deoxycholate.⁶¹⁻⁶³ Although the Gilead Sciences' programme donating AmBisome for leishmaniasis is a partial solution, there is substantial unmet need for LAmB in LMICs, which account for roughly half of the countries of the world. Meanwhile, the down-negotiated price offer for AmBisome to WHO and public sector agencies is limited to cryptococcal meningitis and visceral leishmaniasis in 116 countries, but LAmB is only registered in less than half of these, which presents a barrier to access.^{58,64}

Identifying and addressing the main barriers to LAmB access for LMICs: a call to action

The first barrier to access to LAmB in LMICs is the high price of AmBisome; pricing policies and lack of transparency mean that some LMICs pay more per vial than HICs. As a result, many LMICs have no choice but to adopt the amphotericin B deoxycholate formulation, with negative consequences for patients. Even in the 116 countries in which Gilead Sciences' \$16·25 no-profit price for AmBisome is made available, its use is restricted to just two indications (visceral leishmaniasis and cryptococcal meningitis). The uptake of this price offer is limited due to the complex requirements imposed by Gilead Sciences to prevent diversion of product to other indications and the long delivery times. Thus, in practice, the no-profit price is not widely available. However, the purchase price of LAmB is not the only consideration. The cost of treating adverse events can also increase the total treatment cost substantially. By using LAmB instead of amphotericin B, the need for management and monitoring of amphotericin B-based toxicities and the duration of hospital admission periods are reduced, which could save costs. A recent study showed that a LAmB-based, single-dose regimen for HIV-associated cryptococcal meningitis is cost-effective overall, compared with the standard seven daily doses of amphotericin B deoxycholate formulation, with a further cost reduction of \$128 per life-year saved in Malawi; similar results were found in Uganda, Zimbabwe, South Africa, and Botswana.⁶⁵ The largest proportion of the total cost for both groups of the study was due to hospitalisation, at 42% for the LAmB group and 48% for the amphotericin B

deoxycholate formulation group. The study authors suggested that, outside of the study, shorter hospitalisation times might be possible for the LAmB treatment, which could decrease costs further,⁶⁵ highlighting that a safer product has the potential for a greater cost-reducing effect. The study found that antifungal drugs accounted for 25% and 13% of the total treatment cost for the LAmB and amphotericin B deoxycholate formulation groups, respectively. The study found that fluctuations in drug prices strongly affect economic outcomes, and thus affordable LAmB pricing (such as the no-profit price of AmBisome) is key to ensuring access.⁶⁵

The second barrier to access to LAmB in LMICs is that there are few alternative suppliers to Gilead Sciences. Regulatory requirements for generic registration of LAmB are now clear and there are currently no patent barriers.⁶⁶ However, given the large and lucrative market in HICs, the immediate priority for generic LAmB manufacturers has been entering HIC markets. There are several challenges that need to be addressed collectively before generic market entrants would be successful in LMICs. The first is the need to increase production capacity to supply LMICs as well as the more commercially attractive HICs. To address issue, Unitaid has launched an expression of interest for generic LAmB manufacturers, with the objective of bringing quality-assured generic LAmB to LMICs at an affordable price.⁶⁷ The expression of interest, managed in collaboration with Clinton Health Access Initiative and Drugs for Neglected Diseases Initiative, aims to deploy an incentive package to deliver the access objectives for a quality-assured product. However, there might be a need to explore complementary incentives through other mechanisms, such as volume guarantee from an organisation such as MedAccess, to attain an affordable, high-quality product, while guaranteeing a reliable volume of product for manufacturers.⁶⁸

The third barrier to access to LAmB in LMICs is the absence of regionally or internationally coordinated efforts, involving national governments, international organisations, and civil society, to finance, procure, register, introduce, and deliver optimal LAmB formulations across multiple indications and, therefore, multiple national disease programmes. Regional initiatives, such as the pooled procurement mechanism by the Pan American Health Organization, could play a major role by aggregating demand, facilitating forecasting, and supporting necessary policy changes and strategic decision making.⁶⁹ LAmB will need to be included in national treatment guidelines, essential medicines lists, and national tender or procurement processes. To ensure broader access, beyond donor programmes, each generic LAmB product will need to be registered in all relevant countries and regions. Also, health-care workers will need to be trained on the appropriate use of LAmB because, despite a lower

For more on the **British National Formulary** see <https://bnf.nice.org.uk/>

For more on the **South African Medicine Price Registry** see <http://www.mpr.gov.za/>

For more on the **Brazilian Ministry of Health** see <https://www.gov.br/saude/en>

For more on **RxMediaPharma** see <https://www.eczanet.com/>

toxicity profile than amphotericin B deoxycholate formulation, it still requires intravenous administration and some degree of monitoring. Sound technical cooperation is required to support countries and communities in this process.

Finally, on pricing, generic competition, and the true cost of care: it is possible that the current no-profit price offered by Gilead Sciences will be challenging for generic companies to compete with, at least initially. It will take time for generic producers to manufacture at a scale that could enable them to offer the most competitive price. The only way out of this conundrum will be to have clarity and transparency about the cost of production, including the cost of goods. Only then will a fair, reasonable, and sustainable price be possible to define, allowing governments and other funders to make informed purchasing decisions.

Conclusion

There is a great need for LAmB in LMICs, especially in view of its better toxicity profile that means it could be easier to use in situations with low infrastructure and workforce resources. However, our analysis suggests that LAmB is not widely available nor affordable in many countries. To change the situation, we believe that entry of more LAmB suppliers to the global market could contribute to affordable and equitable access to LAmB, especially for LMICs.

Contributors

JSFL outlined the first draft of the manuscript, led the manuscript narrative, and contributed to drafting and finalisation. RMC, JR, MM, CR, DLNG, JJO, and HYC were involved in conceptualisation and the writing and editing process. JSFL, JR, RAK, and LHC contributed to data collection and analysis. CPC, AR, ECC, JB, JNJ, NF, NG, OS, and RAK contributed to the development, and writing and editing of the manuscript from first draft onwards. IR was involved in project conceptualisation and supervision. All authors accept responsibility for the decision to submit for publication.

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