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Global access to antifungal therapy and its variable cost

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Background: Antifungal therapy saves lives, if given early in life-threatening invasive infection, and also greatly reduces morbidity in hundreds of millions of patients worldwide.

Objectives: We have partially mapped by country systemic generic antifungal drug registration, availability and daily cost for intravenous deoxycholate amphotericin B (50 mg), flucytosine (5 g), oral fluconazole (750–800 mg) and oral itraconazole (400 mg).

Methods: Multiple publically available resources and local country contacts provided data for 159 countries with populations >1 million.

Results: Amphotericin B is not licensed in and unavailable in 22 of 155 (14.2%) and 42 of 155 (27.1%) countries, respectively, representing an unserved population of 481 million. The daily price of deoxycholate amphotericin B varied from <$1 to $171. Fluconazole was licensed in all 141 (88.6%) countries for which data were available although 2 countries appear wholly dependent on the Diflucan® Partnership Program, which is restricted to HIV/AIDS patients. The daily price of fluconazole varied from <$1 to $31. Itraconazole is not licensed in and unavailable in at least 3 of 123 (2.4%) and 5 of 125 (4.0%) countries, respectively, representing an unserved population of at least 78 million. The daily price of itraconazole varied from <$1 to $102. Flucytosine is not licensed in and is unavailable in 89 of 125 (71.2%) and 95 of 125 (76.0%) countries, respectively, representing an unserved population of 2898 million. The daily price of flucytosine varied from $4.60 to $1409.

Conclusions: National governments without access to antifungal drugs should address this health system deficiency urgently to improve clinical outcomes from serious fungal disease. The variability in the price of antifungals between countries is striking.

Introduction

Invasive fungal infections are almost always fatal without treatment.[1,2] The first systemic antifungal agent, amphotericin B, was introduced in the late 1950s and is still the initial agent of choice for several key fungal infections, including cryptococcal meningitis, disseminated histoplasmosis and mucormycosis.[3] The second intravenous agent introduced was flucytosine in the late 1960s, which still plays a critically important role in the initial therapy of cryptococcal meningitis.[4] Ketoconazole has been superseded by fluconazole, introduced in 1990, closely followed by itraconazole in 1991. The azoles provided the first oral antifungal options for patients with multiple different fungal infections, including candidosis, aspergillosis and histoplasmosis. These antifungal agents have transformed outcomes for millions of patients infected by fungi. Amphotericin B, flucytosine and fluconazole are on the Essential Medicine List (EML) issued by the WHO.[5]

In 2013, Loyse *et al.*[6] documented the unavailability and local costs of flucytosine and amphotericin B in 10 countries with a high burden of cryptococcal meningitis in Africa. Neither drug was available in Ethiopia, Democratic Republic of Congo, Guinea, Cameroon or Tanzania. Flucytosine was also not available in Swaziland, South Africa, Uganda, Kenya or Sudan. These deficiencies in antifungal access alerted the global health community to the problems of antifungal access generally.

The Global Action Fund for Fungal Infections (GAFFI) was set up as an international foundation in 2013 to provide a public health voice for current and future patients with fungal disease. One of four key goals for GAFFI is access to antifungal therapy for everyone with fungal disease, as outlined in the 10 year Roadmap '95-95 by 2025'.[7] To this end we have mapped in each country, regulatory approval, availability, listing as an Essential Drug, formulation, dose and cost of amphotericin B, flucytosine, fluconazole and itraconazole, as the most important generic antifungals for life-threatening fungal disease. Terbinafine has little utility for life-threatening infections, although it plays a major role in the treatment of cutaneous infection. Likewise voriconazole, posaconazole and the three echinocandins caspofungin, micafungin

and anidulafungin are not yet or only just becoming generic and so have not been mapped yet.

Methods

We sought data for all countries with populations >1 million (n=159). For this purpose, governed territories were included as part of the governing country, i.e. Macau as part of China; Greenland as part of Denmark, French Guiana as part of France. Baseline information on drug registration, availability and pricing was obtained from numerous sources, including Martindale, the Monthly Index of Medical Specialities (MIMS), the WHO EML, the Diflucan® Partnership Program (DPP), Health Action International and published literature.[5,8–10] We attempted to fill gaps in the data through extensive personal communication (see Acknowledgements), with data being preferentially sought from health professionals of individual countries where possible. We also searched the web and found individual country sources for Afghanistan, Albania, Argentina, Armenia, Australia, Bahrain, Bolivia, Bosnia and Herzegovina, Cameroon, Colombia, Costa Rica, Croatia, Cuba, Cyprus, Czech Republic, Denmark, Ecuador, Eritrea, Ethiopia, France, Georgia, Germany, Ghana, Greece, Hungary, Ireland, Israel, Kuwait, Latvia, Lebanon, Lithuania, Malaysia, Mauritania, Morocco, Myanmar, the Netherlands, New Zealand, Nicaragua, Nigeria, Norway, Paraguay, Peru, Poland, Portugal, Singapore, Slovakia, Slovenia, Spain, Sweden, Trinidad and Tobago, and Turkey. We identified exports from India using 2016 records from Zauba[11] and inferred registration if an export took place to that country for itraconazole and fluconazole.

When a formulation was found in a country, it was listed as registered unless there were additional conflicting data to suggest otherwise; for example, the drug may have been illegally imported and sold. Similarly, drugs were listed as registered if they were found on the WHO National EML for that country. A drug was not considered to be available until country contacts or pharmaceutical databases confirmed that purchase was possible. We have identified separately charity donations such as the DPP for expanded access, although fluconazole's use is restricted to some HIV-infected patients.

Lowest, average and highest daily treatment costs were compiled based on recommended dosages of each drug for commonly treated serious infections (Table 1). For fluconazole we accepted any of the commonly used tablet formulations, resulting in a ranged, aggregated, total dosage for daily treatment costs. This is because 150 mg tablets and capsules are commonly used alongside 50, 100 and 200 mg formulations, resulting in daily doses of between 50 and 800 mg. We excluded intravenous preparations of fluconazole or itraconazole from our study, but accepted any form of flucytosine due to the scarcity of its availability (and equivalent bioavailability regardless of route of administration). Dual-purpose creams and tablets (e.g. Canesten Duo) and formulations mixed with other medications were also excluded. Data are current to March 2016. Prices were converted into US$ at the date of information receipt using exchange rates posted on Google. Some countries legislate for additional dispensing charges such as South Africa (5%–46% of drug price). These are not reflected in our price estimates. Where countries have a special price model for generics (i.e. Norway) these prices are used preferentially rather than pharmacy retail or maximum prices. Data were compiled in a multi-sheet Excel file, with explicit version control rules, and displayed using StatPlanet (StatSilk, Australia) on the GAFFI website (http://www.gaffi.org/antifungal-drug-maps/).

Individual country-level and worldwide population data were obtained from Google Public Data.[23] Where a country had no registration, or registration with confirmed unavailability, its population was added to a list. The sum of all unavailable/unregistered countries for a given drug was then compared against the world population to derive a figure for people unable to access that drug.

Results

Multiple data for each antifungal agent are summarized in Table 2. We were able to access data from every country with a population of >1 million, for at least one agent (Table 2). Data on licensing and availability are missing for some countries because of a lack of information from our multiple sources, and this is indicated in Table 2 and in Figures 1–4. A complete listing is available of licensing and availability online at http://www.gaffi.org/antifungal-drug-maps/. We have calculated the minimum populations unable to access each antifungal medication (Table 2) assuming that all countries where data are unavailable have access to that agent, which is unlikely. We were unable to access price data for many countries—what is available is shown in Figure 5 for fluconazole

Table 1. Indications and daily doses for fluconazole, itraconazole, amphotericin B and flucytosine

Drug	Usage	Guideline daily dosage	Reference(s)	Aggregated dosage
Fluconazole	invasive candidosis	400 mg	12	750–800 mg (oral)
	cryptococcal meningitis—induction	800 mg	13	
	cryptococcal meningitis—maintenance	200 mg	13	
	vulvovaginal and oral candidosis	150 mg	14, 15	
Itraconazole	histoplasmosis	200–600 mg	16	400 mg (oral)
	sporotrichosis	200–400 mg	17	
	blastomycosis	200–600 mg	18	
	Talaromyces marneffei infection	400 mg	16	
	chronic or invasive aspergillosis	400–600 mg	19	
	allergic aspergillosis	400 mg	19, 20	
Amphotericin B	cryptococcal meningitis	0.7–1.0 mg/kg	13	50 mg (intravenous)
	histoplasmosis	1.0 mg/kg	16	
	invasive and chronic aspergillosis	1.0 mg/kg	19, 21	
	mucormycosis	1.0–1.25 mg/kg	22	
Flucytosine	cryptococcal meningitis	100 mg/kg	13	5 g (oral or intravenous)

Table 2. Licensing and availability of each antifungal agent by country

Disease/status	Intravenous only amphotericin B	Intravenous and oral		
		fluconazole	itraconazole	flucytosine
Countries where not licensed	22/155 (14.2%)	0/151	3/123 (2.4%)	89/123 (72.4%)
Countries where not available	42/155 (27.1%)	0/143[a]	5/125 (4.0%)	94/120 (78.3%)
World population unable to receive antifungals[b]	481 million (6.62%)	none	78 million (1.07%)	2898 million (39.9%)

[a]Availability in five countries is limited to the DPP (HIV only).
[b]Assumes that all countries for which we have no data have access, which is unlikely.

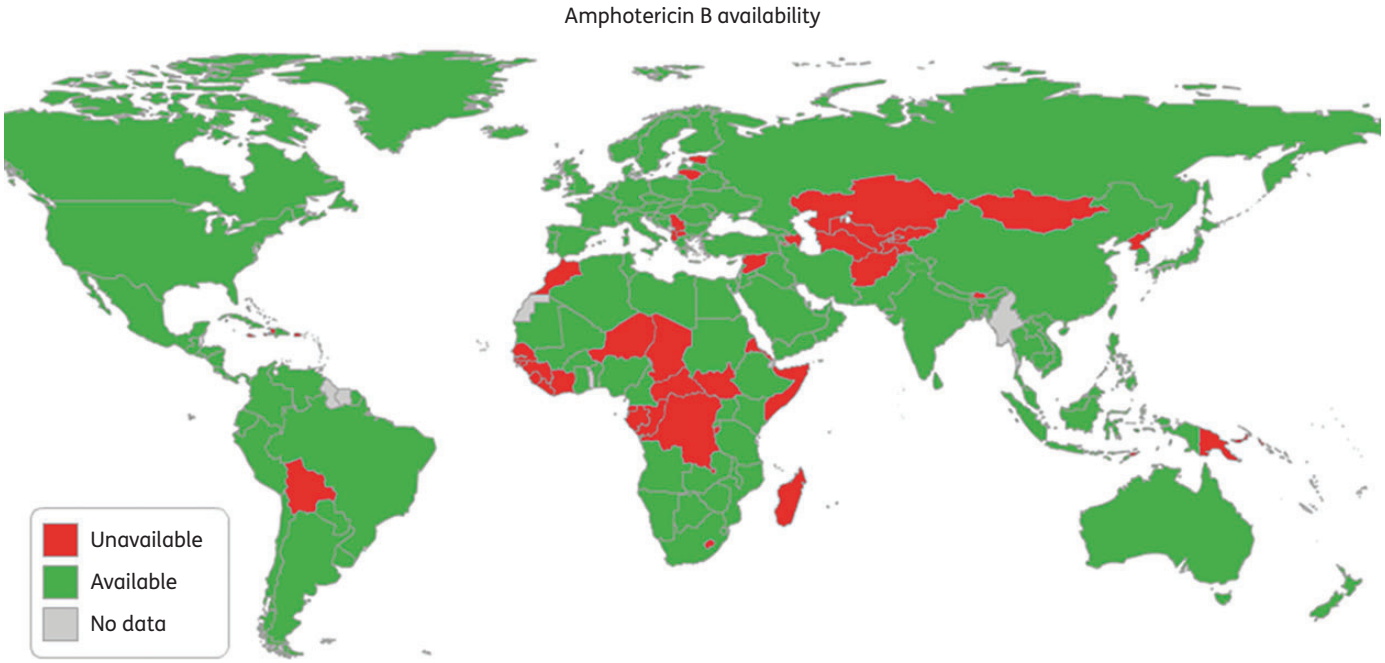

Figure 1. Amphotericin B availability by country in 2016. Jordan, Libya and Iran only have lipid-associated amphotericin B available, and these are included. Red=not available, green=available and grey=no data. This figure appears in colour in the online version of *JAC* and at http://www.gaffi.org/antifungal-drug-maps/ and in black and white in the print version of *JAC*.

and online for the other agents at http://www.gaffi.org/antifungal-drug-maps/.

Amphotericin B

Amphotericin B is not licensed in 22 countries and is not available in 42 countries. About 481 million people, 6.6% of the global population, have no access to amphotericin B (Table 2). Amphotericin B is prepared in a deoxycholate formulation and for the last 20 years as lipid-associated formulations to reduce adverse events, nephrotoxicity in particular. We were unable to determine licensing status for amphotericin B for 2 countries and availability for 4 countries. Amphotericin B is listed on the EML in 11 countries, but our data are very incomplete.

There are many different amphotericin B preparations on the market. The deoxycholate formulation is generic, and made by a small number of manufacturers, usually as 50 mg Fungizone®. We have also captured the number of different preparations of each agent available in each country (see dynamic graphic at http://www.gaffi.org/antifungal-drug-maps/. The country with the largest number of amphotericin B formulations is India (n=25), followed by Brazil (n=9), Argentina (n=6) and Thailand (n=5).

We have compared the lowest cost of a single dose of 50 mg by country, which often equates to a single day's dose. Daily prices for 50 mg of <$1 were found in Zambia, the Netherlands, Russia and Chile. High prices were seen in Canada ($171.47) (liposomal amphotericin B was $118.45), Finland ($85.44), Germany ($81.66), Hungary ($28.73), Bulgaria ($25.38), Libya ($20.57), Egypt ($18.14), Iraq ($15.17), Israel ($15.83), Malawi ($14.08), Vietnam ($13.76), Brazil ($13.50), Costa Rica ($12.20) and South Korea ($11.54). The various lipid-associated and liposomal amphotericin B preparations are all higher in price than the deoxycholate formulation (apart from Canada), with considerable variations between countries. Some countries, notably Jordan, Libya and

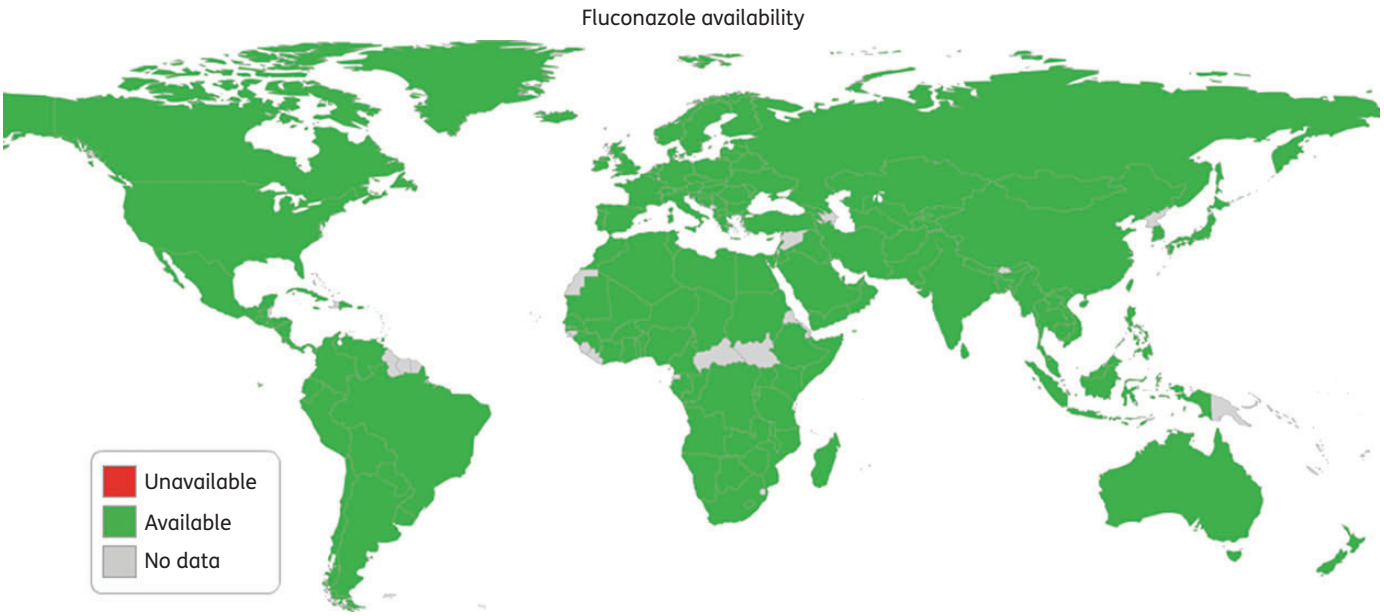

Figure 2. Oral fluconazole availability by country in 2016. Red = not available, green = available and grey = no data. This figure appears in colour in the online version of *JAC* and at http://www.gaffi.org/antifungal-drug-maps/ and in black and white in the print version of *JAC*.

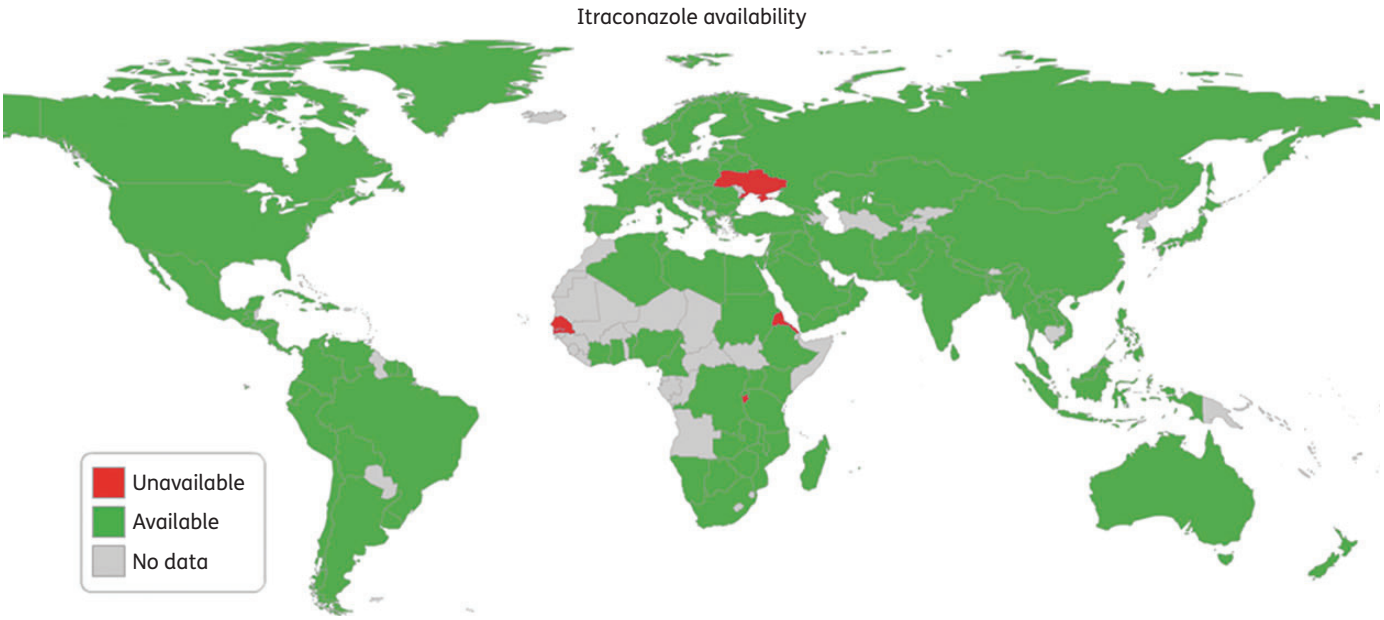

Figure 3. Oral itraconazole availability by country in 2016. Red = not available, green = available and grey = no data. This figure appears in colour in the online version of *JAC* and at http://www.gaffi.org/antifungal-drug-maps/ and in black and white in the print version of *JAC*.

Iran, only have lipid-associated amphotericin B on the market. We have not attempted comprehensive data collection for these non-deoxycholate formulations and so they are not presented here.

Fluconazole

Fluconazole was registered and available in all countries for which we received data (Table 2). Its availability in Botswana and Lesotho appears to be completely reliant on the DPP with Pfizer, which restricts usage to HIV-infected patients. In Benin, Burkina Faso, Cambodia, Cameroon, Chad, Congo, Cote d'Ivoire, Dominica, Ghana, Moldova, Togo, Trinidad and Tobago, and Zimbabwe, the DPP is a major source of supply.

The number of fluconazole generic preparations is very large. In many countries, the presence of multiple different pack sizes, strengths and trade names makes analysis and summary of

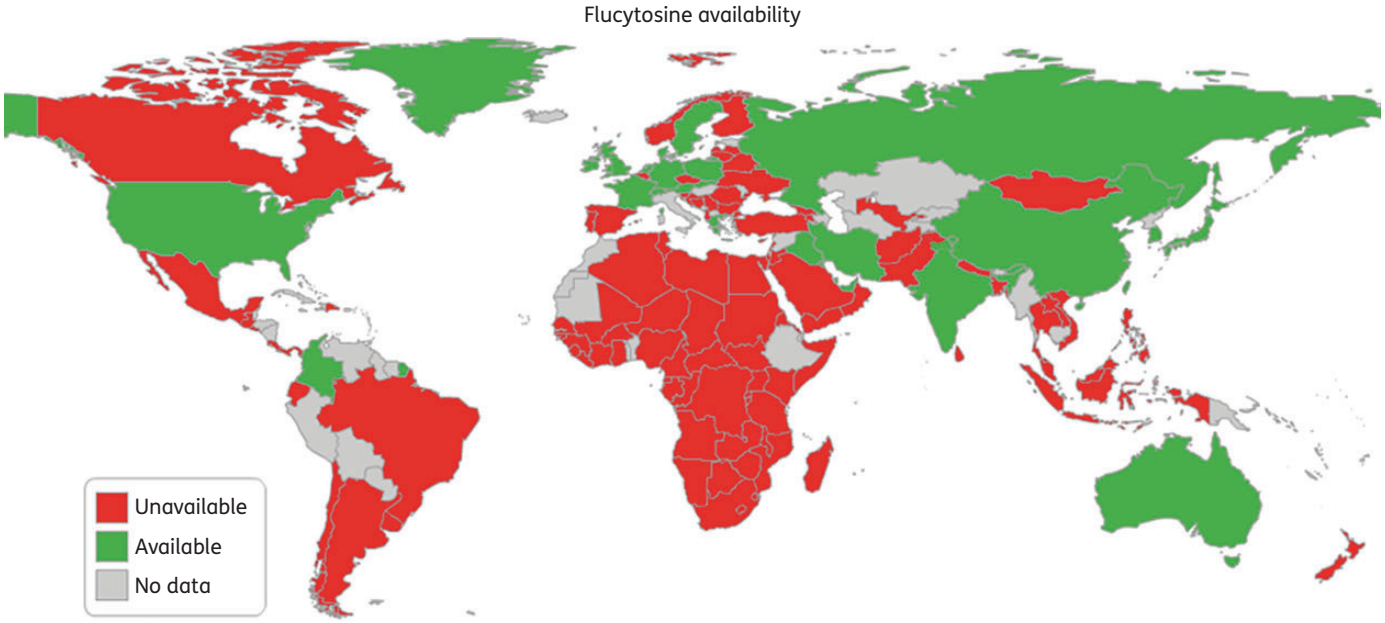

Figure 4. Intravenous and/or oral flucytosine availability by country in 2016. Red=not available, green=available and grey=no data. This figure appears in colour in the online version of *JAC* and at http://www.gaffi.org/antifungal-drug-maps/ and in black and white in the print version of *JAC*.

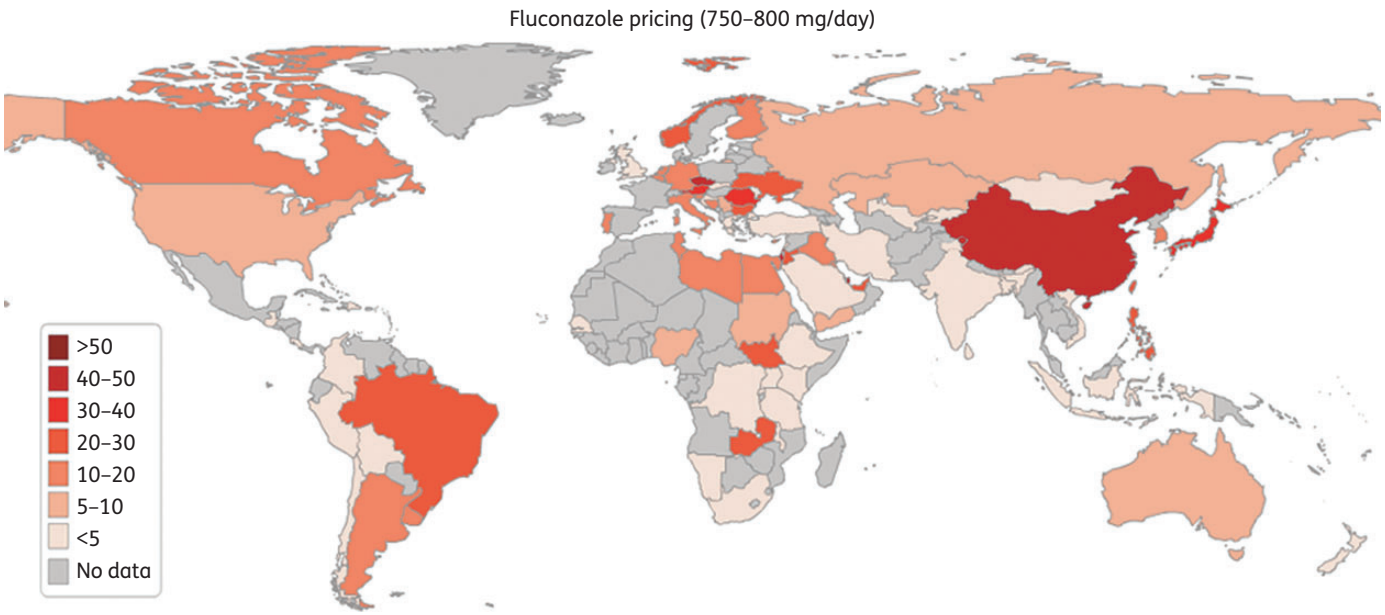

Figure 5. Lowest daily cost of fluconazole treatment based on 750–800 mg by country in 2016. All prices in US$, converted from local currency as data received from 2013 to 2016. Grey=no data. This figure appears in colour in the online version of *JAC* and at http://www.gaffi.org/antifungal-drug-maps/ and in black and white in the print version of *JAC*.

availability complex. The most frequent formulation is the 150 mg capsule used as a single dose for vaginal candidosis—there are 8 countries with only this formulation: Cuba, Jordan, Kyrgyzstan, Qatar, South Sudan, Tanzania, Vietnam and Yemen.

Despite fluconazole being listed as an Essential Drug by the WHO since 1999, several countries have not placed it on their own country's Essential Medicine List, even if it is available locally, notably Colombia, Gabon, Poland, Serbia, Lebanon, Indonesia and Malaysia, as well as some smaller countries, Bhutan and Surinam. Unfortunately, our data are markedly incomplete for this data field.

We have elected to compare prices for the most commonly recommended induction dose of fluconazole for cryptococcal

meningitis—750–800 mg daily. The range in lowest country daily price for this treatment varies from $0.13 in Ethiopia to $30.52 in Australia. Other countries with costs <$1 a day for this high dose include Zambia, Peru, India, Lebanon, Costa Rica, Vietnam, Iran, Namibia, UK, Sri Lanka, Malawi, Guatemala and Bangladesh. Countries with a daily cost in excess of $20 include Austria ($30.22), Brazil ($25.00), Jordan ($27.7), the Philippines ($23.86), Ukraine ($20.00) and the United Arab Emirates ($27.90).

Itraconazole

Itraconazole is not registered or available in Eritrea, Gambia and Senegal, and is registered but not available in Burundi and Ukraine. At least 78 million people have no access to itraconazole (Table 2).

Itraconazole is also available in generic formulations, but almost all oral preparations are 100 mg capsules. Greece has 32 different formulations on the market, probably many made by the same generic manufacturer. Mexico has 25, South Korea 22, Germany and Pakistan 16, Indonesia 15, Brazil 13, and Italy and the Netherlands 11 different preparations.

The standard dose of oral itraconazole for any form of aspergillosis and coccidioidomycosis is 400 mg daily, and we have used this dose to compare prices. Countries with costs <$1 a day for itraconazole therapy include Sri Lanka, Vietnam, Lebanon, Bangladesh, Turkey, Uganda and Taiwan. In contrast, high daily prices are found in Sweden ($98.15), USA ($28.00), Denmark ($23.63), Bulgaria ($22.37), Nigeria ($19.36), Norway ($18.59), Colombia ($15.24), Guatemala ($14.91), South Africa ($14.81), Brazil ($14.23), Libya ($13.58), Zambia ($13.33), Japan ($13.02), Uruguay ($12.95), the United Arab Emirates ($12.36), Czech Republic ($11.90), Finland ($11.29), Australia ($11.17), Russia ($10.83), Namibia, ($10.15), Germany ($10.80), Iraq ($10.57) and Belgium ($10.39). In some countries the contrast between the most expensive product, usually Sporonox®, and the most inexpensive generic is substantial. In Russia, for example, Orungal® is sold for $39.50 per daily treatment, compared with Canditral® for $4.35. In many other countries the ratio between the most costly and least expensive itraconazole product is 3 or 4 times.

In contrast to the other three antifungals described here, itraconazole is not listed by the WHO as an essential medication, yet is included as such by many countries, including Brazil, Ecuador, Uruguay, Peru, Cuba, Ghana, Angola, Lesotho, Tanzania, Madagascar, Egypt, Tunisia, Slovenia, Bulgaria, Albania, Syria, Iran, Nepal, Thailand, Vietnam and New Zealand. There are many countries for which no data are available for our dataset for this field.

Flucytosine

Flucytosine is not licensed in at least 89 countries and is not available in at least 94 countries. At least 2898 million people, almost 40% of the world's population (Table 2), do not have access to flucytosine for cryptococcal meningitis. Intravenous flucytosine is provided as a 250 mL bottle at a 10 mg/mL concentration. Typically 50% of a bottle will be administered three or four times daily. We have assumed the use of four bottles daily for treatment, although this may be excessive if weight is low or renal function poor. The daily price for intravenous therapy was obtained for three countries: Australia ($278), Greece ($43.62) and Russia ($29.08). Oral therapy was calculated as 5 g daily dose (approximately 100 mg/kg in four doses). Daily prices varied from $1409 (USA),[24] $626 (United Arab Emirates) to $8.12 (Greece). In contrast to the United Arab Emirates, the price in Kuwait is $10.97 and in Qatar $17.00. The daily price in South Korea has fallen precipitously since we first accessed pricing information, from $1320 to $12.74, with a new supplier. There appears to be no country in Africa—the continent with the largest burden of cryptococcal meningitis—with flucytosine both licensed and available.

Discussion

Fungal disease probably kills 1.5–2.0 million people each year, of whom over 700 000 are HIV infected,[7] a similar number to the deaths caused individually by AIDS,[25] TB,[26] diarrhoeal disease[27] and diabetes,[28] and rather more than road injury.[29] At least half, and probably two-thirds, of fungal deaths are avoidable deaths, if treatment were given. An estimated 17% of AIDS deaths are attributable to cryptococcal meningitis.[30] Survivors of cryptococcal meningitis, invasive aspergillosis and candidiasis, disseminated histoplasmosis and *Pneumocystis* pneumonia usually make a full recovery, allowing long and fulfilling lives, if their underlying condition remits, which it often does.

The lack of amphotericin B impacts on the outcomes of several infections, notably cryptococcal meningitis, disseminated histoplasmosis, fluconazole-resistant invasive candidiasis, mucormycosis and others.[4] The lack of flucytosine reduces the primary response rate and culture conversion to negative in cryptococcal meningitis, increasing mortality by 10%–25% over 3–12 months.[31] The complete lack of availability of both amphotericin B and flucytosine decreases survival rates from ~75% to ~30% at 3 months in Africa.[32,33] The typical overall drug cost of combined amphotericin B and flucytosine for 2 weeks of induction therapy are ~$450, although this varies widely as our data indicate. Assuming that only 40% of cryptococcal meningitis patients are missed with the antigen 'screen and treat' programme, and that both amphotericin B and flucytosine are available to all, over 50 000–70 000 lives would be saved annually if both drugs were available and used.[34] Availability of early antigen diagnosis of disseminated histoplasmosis in AIDS and amphotericin B and/or itraconazole could reduce deaths by over 40 000 annually.[34]

Fluconazole has a special place in the management of AIDS patients, reducing the discomfort and morbidity of oral and oesophageal candidiasis before treatment of the HIV infection itself. As it can be administered orally and has low toxicity, fluconazole quickly established itself as the agent of choice for these conditions, and also demonstrated efficacy against cryptococcal meningitis; hence, there were many international calls for greater access to this therapy. Pfizer generously established the DPP around the millennium and continues to provide fluconazole for the management of, in particular, cryptococcal meningitis to many countries. Some of the economies and health systems of these countries have grown substantially, including Trinidad and Tobago (GDP per capita $18 372 in 2013), Botswana (GDP per capita $7315 in 2013) and South Africa ($6617 per capita in 2013), and, in these, it is likely that the DPP interferes with the commercial importation of fluconazole to treat all those who

need it, not just HIV-infected patients. A phased withdrawal of the DPP is required in countries with sufficient resources and buying power to import fluconazole at very low prices, as seen in Peru, Lebanon or Costa Rica, to broaden access to the whole population. However, withdrawal would not be ethical if fluconazole remains unregistered. Clearly, a substantial lead time for withdrawal from the DPP by any country and affordable pricing for fluconazole are prerequisites for a successful transition to a broader supply.

Itraconazole was the first oral agent with efficacy for aspergillosis and quickly became the oral agent of choice for histoplasmosis, blastomycosis and sporotrichosis,[2] as well as eosinophilic folliculitis in AIDS.[15] Fluconazole has no activity against *Aspergillus* spp. and is inferior to itraconazole for the latter three indications. Itraconazole is also superior to sulphonamides for paracoccidioidomycosis and has fewer side effects.[35] Over 10 million people have allergic or chronic pulmonary aspergillosis[7] and most of these could benefit from long-term itraconazole therapy.[36,37] Voriconazole is probably superior to itraconazole for invasive aspergillosis, and posaconazole is superior for antifungal prophylaxis in leukaemia,[4] but both are unaffordable for most patients and healthcare systems, and have not been compared for chronic and allergic aspergillosis. Itraconazole is not yet on the WHO EML in 2016, although it is on country EMLs in at least 21 countries. We have not mapped itraconazole oral suspension which is the preferred preparation for AIDS, leukaemia and bone marrow transplant patients, for children and for those with fluconazole-resistant oral and oesophageal candidiasis. This is a future task, particularly if itraconazole is placed on the WHO EML.

There are many limitations to our study. The most overt is missing data—despite nearly 3 years of attempting to access all antifungal data from multiple sources, we have not been able to be fully comprehensive. No central repository holds all the key data on drug licensing for all countries, on inclusion on country EMLs or even on all manufacturers of these agents. For over 60 countries, data were provided by health professionals in those countries from their local sources (see Acknowledgements). While availability is clearly identified through this route, and most of the preparations also, some are likely to have been missed. In addition, prices fluctuate over time and between hospitals, and may not be fully representative of that country. The currency conversion to US$ was done as the data arrived (from July 2013—March 2016), which will have materially changed in some instances. The prices may or may not include local discounts and do not include additional dispensing charges, which are typically unavoidable. Some prices were approximate and our data are presented to the cent, which is potentially misleading but unavoidable with the methodology used. Likewise we have almost certainly not captured all country-wide generic price controls. While some preparations may be less expensive than others, we have not been able to verify that each product is a *bona fide* registered product on that market, subject to the usual regulatory controls. It has not been possible to check that all products are authentic and of high quality.

Lack of access to antifungals, and their unaffordability, has a profound negative and often fatal impact on those with serious and life-threatening fungal infections. To rectify this situation major movement is required on behalf of both companies manufacturing and supplying drugs and government regulators, to fast-track applications of well-established antifungal medicines. Engagement of pharmaceutical companies requires a detailed understanding of the market opportunity, price stability, provision of the appropriate diagnostics and physician training.

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Transparency declarations

D. W. D. holds Founder shares in F2G Ltd, a University of Manchester spin-out antifungal discovery company, holds Founder shares in Novocyt, which markets the Myconostica real-time molecular assays, and has current grant support from the National Institute of Health Research, the MRC, the Global Action Fund for Fungal Infections and the Fungal Infection Trust. He acts or has recently acted as a consultant to Astellas, Sigma Tau, Basilea, Scynexis, Cidara and Pulmocide. In the last 3 years, he has been paid for talks on behalf of Astellas, Dynamiker, Gilead, Merck and Pfizer. He is also a member of the Infectious Diseases Society of America Aspergillosis Guidelines and European Society for Clinical Microbiology and Infectious Diseases Aspergillosis Guidelines groups. All other authors: none to declare.

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