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Received: 7 October 2018 | Revised: 28 March 2019 | Accepted: 14 March 2019

DOI: 10.1111/myc.12912

ORIGINAL ARTICLE

WILEY mycoses Diagnosis, Therapy and Prophylaxis of Fungal Diseases

Systemic antifungal drug use in Belgium—One of the biggest antifungal consumers in Europe

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Funding information
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Summary

Background: Reports on the consumption of systemic antifungal drugs on a national level are scarce although of high interest to compare trends and the associated epidemiology in other countries and to assess the need for antifungal stewardship programmes.

Objectives: To estimate patterns of Belgian inpatient and outpatient antifungal use and provide reference data for other countries.

Methods: Consumption records of antifungals were collected in Belgian hospitals between 2003 and 2016. Primary healthcare data were available for the azoles for the period 2010-2016.

Results: The majority of the antifungal consumption resulted from prescriptions of fluconazole and itraconazole in the ambulatory care while hospitals were responsible for only 6.4% of the total national consumption and echinocandin use was limited. The annual average antifungal consumption in hospitals decreased significantly by nearly 25% between 2003 and 2016, due to a decrease solely in non-university hospitals. With the exception of specialised burn centres, antifungals are mostly consumed at ICUs and internal medicine wards. A significant decline was also observed in the consumption of azoles in primary health care, attributed to itraconazole. The major part of azoles was prescribed by generalists followed by dermatologists.

Conclusions: In spite of the downward trend in annual use of systemic antifungal drugs, Belgium remains one of the biggest consumers in Europe.

KEYWORDS
antifungal agents, hospital, prescription rates, primary care, public health, surveillance

1 | INTRODUCTION

Paralleling an increasing population of immunocompromised patients during the last decades, opportunistic fungal infections gained major importance in health care, resulting in a rise in the consumption of antifungal drugs.[1-4] With the introduction of new antifungals, therapeutic options have been extended and a variety of agents from four different classes can currently be addressed for the treatment of fungal infections: polyenes, azoles, echinocandins and flucytosine. Furthermore, empirical therapy in high-risk patients significantly impacts consumption as illustrated by the high prescription of antifungal drugs in ICUs and haematology-oncology units.[5-7]

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The consumption of antifungals also influences the distribution of microbial species and reduces the susceptibility of target pathogens.[8-12] In order to follow up trends and to minimise antifungal selective pressure, consumption monitoring and antifungal stewardship approaches should be implemented on a local and on a national level.[4,6,13]

Geographical differences in fungal species distribution and associated infections may influence the choice of antifungal therapy. The latter should be adapted according to the local epidemiology of fungal pathogens. Hence, it is appropriate to outline the trends in antifungal consumption on different geographical scales.

Limited data exist on the consumption of systemic antifungal drugs on a national level. Data often remain limited to the hospital sector or to a specific hospital unit such as the ICU (due to a high level of consumption).[3,7,14,15] Some studies define the consumption according to locally used doses (prescribed or recommended daily doses), reflecting better actual prescriptions but they are unsuitable for international comparison.[3,5] Other studies do not distinguish between consumption in hospitals versus primary care or report sales data, not adequately expressing the intensity of drug use (treatment incidence).[16]

This study aims to provide nationwide reference data (for benchmarking) by evaluating systemic antifungal consumption patterns in both the ambulatory and hospital care sectors in Belgium. Regarding the latter, separate analyses were performed on university and non-university hospitals and data were also stratified by type of hospital wards (units). Consumption was expressed in defined daily doses (DDD)/1000 patient-days (hospitals) and in DDD/1000 inhabitants per day (ambulant and hospitals).

2 | MATERIAL AND METHODS

National inpatient consumption data on antifungals for systemic use (J02) in the hospital sector (numerator) and number of patient-days (denominator) were based on reimbursement data provided by the Belgian National Institute for Health and Disability Insurance (INAMI-RIZIV) and validated by the Healthcare-Associated Infections and Antimicrobial Resistance service at Sciensano, Belgium.[17] In 2016, approximately 98.6% of the Belgian population had a health insurance equalising reimbursement. Data on not reimbursed use of antifungals were not available. Consumption data were categorised according to the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification index, and the *defined daily doses* (DDD) was applied as unit of measurement to allow standardised and international comparisons.[18]

The following antifungal drugs were available in Belgium, and their consumption data were evaluated in this study: amphotericin B (J02AA01) (the conventional formulation was available until 2010), flucytosine (J02AX01), ketoconazole (J02AB02), fluconazole (J02AC01), itraconazole (J02AC02), voriconazole (J02AC03), posaconazole (J02AC04), caspofungin (J02AX04) and anidulafungin (J02AX06). Consumption was expressed in DDD/1000 patient-days for the period 2003-2016 in hospitals and also in DDD/1000 inhabitants per day (DID) for the period 2010-2016.

A total of 105 acute care hospitals (with slightly varying participation over years, Table S1) provided consumption data annually. Data were available to classify the type of the hospital, the hospitalisation unit and the antimicrobial agent at ATC level five. Annual consumption was expressed as the mean of sum of the antifungal usage per hospital for the year, unit and agent considered. Hospitals were classified according to teaching level: university hospitals (tertiary hospitals, n = 7) and non-university hospitals (n = 98). Consumption data of the following hospitalisation units were included in the analyses: surgery, internal medicine, geriatrics, paediatrics, intensive and non-intensive neonatology, maternity, infectious diseases, burn unit, ICUs and specialised care. A separate analysis was performed on the consumption data of the internal medicine (including the haematology-oncology unit) and the ICUs because highest consumptions generally occur in these units.[19]

For the primary healthcare sector, national data concerning azoles for systemic use (J02AB, J02AC) were available for the period 2010-2016 and expressed in DID. Azoles for systemic use are only available on prescription in Belgium. Consumption data were based on all outpatient drug prescriptions delivered by public pharmacies, reimbursed and provided by INAMI-RIZIV and validated by PharmaNet. Data were available by type of prescriber (specialism) up to ATC level five. Patient gender was also available for ambulant prescriptions. The size of the Belgian population by year was provided by the Belgian Statistical Office and expressed as the number of inhabitants at January the first of that year.[20] Associated costs were also available with a distinction between costs for the patients and costs for the social security system.

All data were handled using Microsoft Excel software, and statistical analyses were performed using the Stata software (StataSE 14, Stata Corp. 2013, College Station, Texas). Trends of antifungal consumption over time were evaluated with the Mann-Kendall test. The Wilcoxon signed-rank test was used to compare differences between university and non-university hospitals as well as between hospital units. *P* values less than 0.05 were considered statistically significant.

3 | RESULTS

3.1 | National inpatient data: hospital-wide consumption

Figure 1 shows an overview of the annual average consumption of systemic antifungals (J02) in Belgian hospitals between 2003 and 2016. The annual average hospital consumption of all systemic antifungal agents decreased significantly ($P < 0.05$) by nearly 25% between 2003 (37.72 DDD/1000 patient-days) and 2016 (28.42 DDD/1000 patient-days). The latter is not equal to the sum of the annual average consumption of the different subclasses because of the variation in the use of these subclasses per hospital (Table S1). Fluconazole was the most prescribed antifungal agent in Belgian

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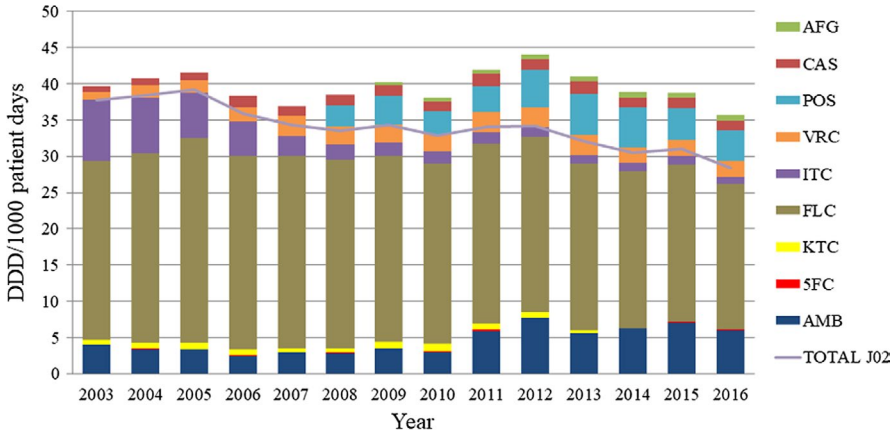

FIGURE 1 Annual average consumption of systemic antifungals (J02) in Belgian hospitals between 2003 and 2016. The annual average consumption is not equal to the sum of the different subclasses. AFG, anidulafungin; AMB, amphotericin B; CAS, caspofungin; DDD, defined daily doses; FLC, fluconazole; 5FC, 5-flucytosine; ITC, itraconazole; J02, antifungals for systemic use; KTC, ketoconazole; POS, posaconazole; VRC, voriconazole

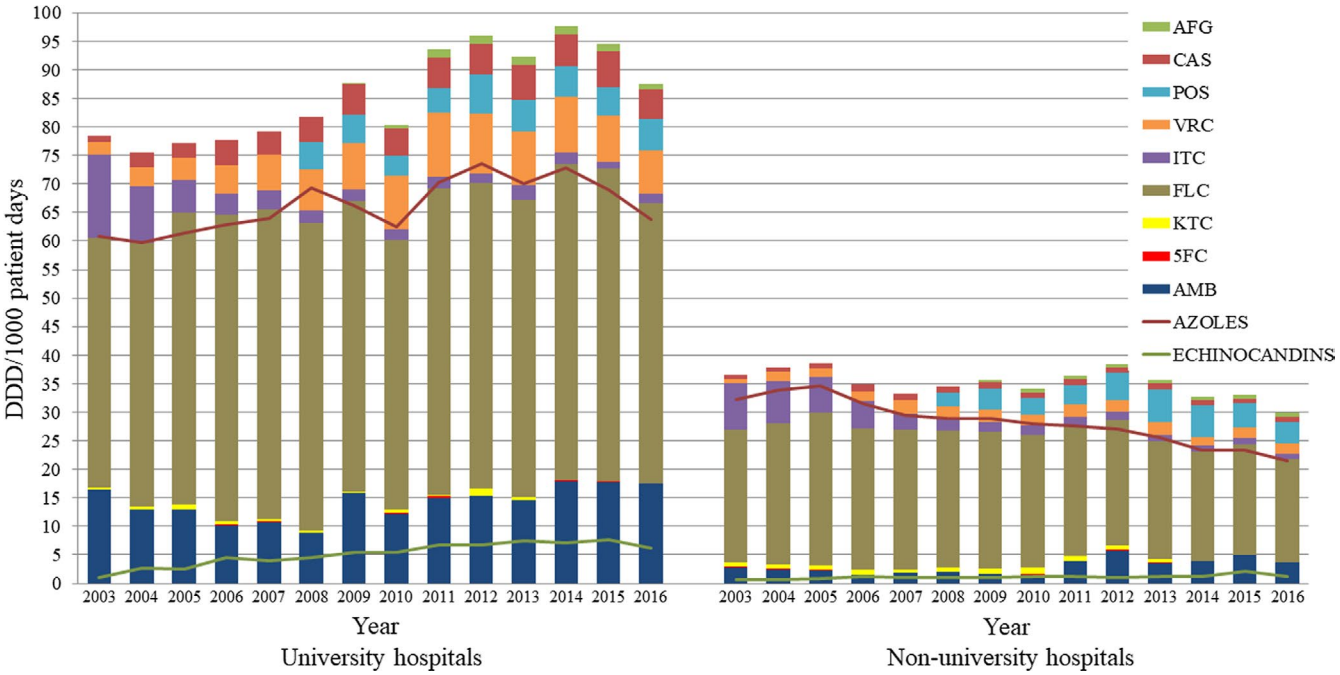

FIGURE 2 Annual average consumption of systemic antifungals (J02) between 2003 and 2016 according to teaching level. The annual average consumption is not equal to the sum of the different subclasses. AFG, anidulafungin; AMB, amphotericin B; CAS, caspofungin; DDD, defined daily doses; FLC, fluconazole; 5FC, 5-flucytosin; ITC, itraconazole; KTC, ketoconazole; POS, posaconazole; VRC, voriconazole

hospitals throughout the period and accounted for almost three-fourth of all prescriptions with an overall mean of 24.60 DDD/1000 patient-days per year. The average fluconazole consumption decreased since 2005 although its relative use (compared to the total consumption) has risen. Posaconazole was the second most consumed agent since its introduction in 2008 with an annual average of 4.26 DDD/1000 patient-days over the years from 2008 to 2016. The annual average consumption of amphotericin B remained below 5 DDD/1000 patient-days until 2010 and then increased and reached a maximum of 8 DDD/1000 patient-days in 2012. The annual average use of itraconazole was 3.05 DDD/1000 patient-days but decreased over time from 8.56 DDD/1000 patient-days in 2003 to 0.95 DDD/1000 patient-days in 2016. In contrast, the consumption of voriconazole increased, although irregularly, between 2003 (0.97 DDD/1000 patient-days) and 2016 (2.23 DDD/1000 patient-days), with an average of 2.27 DDD/1000 patient-days. Caspofungin displayed higher consumption rates compared to anidulafungin, and together, the echinocandins constitute less than 6% of the total hospital consumption of systemic antifungals in 2016 (1.59 DDD/1000 patient-days). The annual average consumption of ketoconazole and flucytosine was both low: 0.76 and 0.08 DDD/1000 patient-days, respectively. Since 2013, the oral formulation of ketoconazole has been withdrawn from the Belgian market.

3.2 | National inpatient data: university versus non-university hospitals

Figure 2 highlights the differences in average annual use of systemic antifungals according to teaching level between 2003 and 2016. Overall mean consumption at university hospitals was almost three

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times higher compared to non-university hospitals. University hospitals consumed on average 66.18 DDD/1000 patient-days of azoles annually and 5.13 DDD/1000 patient-days of echinocandins. In comparison, the latter were 28.28 DDD/1000 patient-days and 1.12 DDD/1000 patient-days, respectively, in non-university hospitals ($P < 0.05$). An increase was noticed in the echinocandin consumption at both university and non-university hospitals ($P < 0.05$). Azole consumption decreased significantly ($P < 0.05$) in non-university hospitals while it increased in university centres, although irregularly ($P < 0.05$). The most important differences between university and non-university hospitals during the 14-year period were observed with amphotericin B (4.8 times more in university hospitals compared to non-university), caspofungin (4.7 times more) and voriconazole (3.9 times more). Fluconazole was the most consumed azole in both types of hospitals and was over two times more applied at university compared to non-university hospitals. The average antifungal consumption in ICUs at university hospitals was 287.72 DDD/1000 patient-days in comparison with 188.99 DDD/1000 patient-days at non-university hospitals.

3.3 | National inpatient data: consumption per department (ICUs and internal medicine)

The annual mean consumption of systemic antifungal drugs in ICUs and internal medicine was 195.21 DDD/1000 patient-days and 47.40 DDD/1000 patient-days, respectively. The average consumption of the six Belgian burn centres was 183.86 DDD/1000 patient-days per year and 154.00 DDD/1000 patient-days per year for the single infectious disease unit. Consumption in other units varied between 1.21 DDD/1000 patient-days (maternity) and 16.51 DDD/1000 patient-days (geriatrics). Figure 3 shows the average annual use of systemic antifungals in ICUs and internal medicine during the period 2003-2016. Fluconazole was the most consumed agent each year in both departments with an average of 150.17 DDD/1000 patient-days per year in ICUs and 32.14 DDD/1000 patient-days per year in internal medicine. Fluconazole consumption peaked in 2005 (169.27 DDD/1000 patient-days) in ICUs but decreased to 113.67 DDD/1000 patient-days in 2016 ($P < 0.05$). A downward trend in fluconazole consumption was also observed in internal medicine, from 31.89 DDD/1000 patient-days in 2003 to 24.85 DDD/1000 patient-days in 2016 ($P < 0.05$). Itraconazole was the second most consumed antifungal drug up to 2005 in both departments but since 2006, amphotericin B took second place with an average use of 39.04 DDD/1000 patient-days per year in ICUs and 8.90 DDD/1000 patient-days per year in internal medicine. The average consumption of voriconazole was respectively 18.11 and 3.80 DDD/1000 patient-days per year in ICUs and in internal medicine. The average use of posaconazole reached 10.42 DDD/1000 patient-days per year in internal medicine, and its relative consumption was four times higher than in ICUs. Caspofungin use in ICUs remained relatively stable during the study period with an average of 9.95 DDD/1000 patient-days per year, similar to anidulafungin (9.96 DDD/1000 patient-days

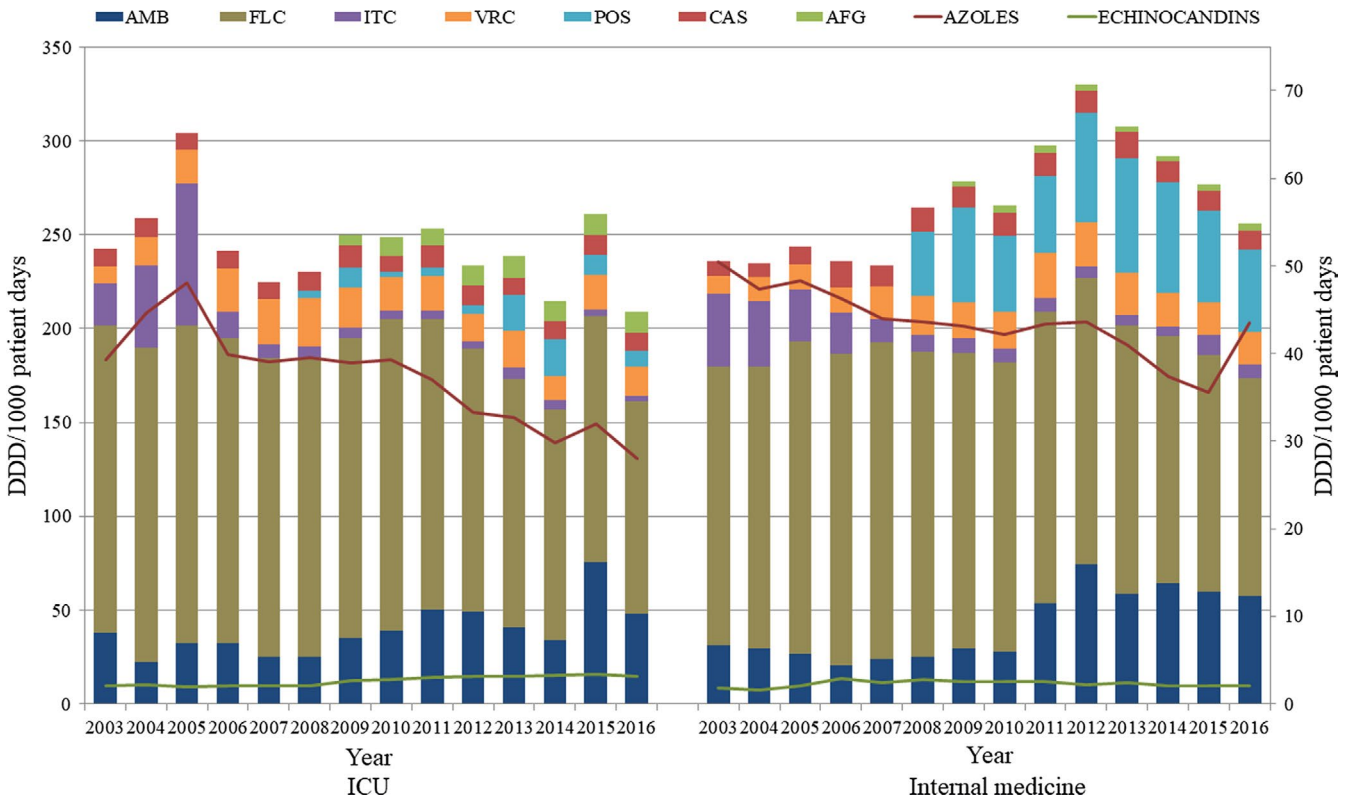

FIGURE 3 Annual average consumption of systemic antifungals (J02) in ICUs and internal medicine during 2003-2016. The annual average consumption is not equal to the sum of the different subclasses. AFG, anidulafungin; AMB, amphotericin B; CAS, caspofungin; DDD, defined daily doses; FLC, fluconazole; ICU, intensive care unit; ITC, itraconazole; POS, posaconazole; VRC, voriconazole

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TABLE 1 Average annual consumption of azoles in ambulatory care (reimbursement data) in Belgium between 2010 and 2016 in defined daily doses per 1000 inhabitants per day (DID)

	DID					
Year	Fluconazole	Itraconazole	Ketoconazole	Voriconazole	Posaconazole	Total azoles
2010	0.680	0.683	0.083	0.006	0.003	1.455
2011	0.704	0.667	0.072	0.007	0.003	1.453
2012	0.709	0.633	0.064	0.007	0.004	1.419
2013	0.706	0.597	0.049	0.008	0.005	1.366
2014	0.706	0.580	0.000	0.008	0.005	1.299
2015	0.701	0.553		0.008	0.004	1.267
2016	0.696	0.542		0.007	0.005	1.250
Average	0.701	0.607	0.038	0.007	0.004	1.357

per year). In contrast, the average consumption of caspofungin (2.4 DDD/1000 patient-days per year) in internal medicine was over t times higher than anidulafungin (0.72 DDD/1000 patient-days per year). Ketoconazole (when available) and flucytosine were rarely used in both units.

3.4 | National outpatient data

Table 1 provides an overview of the consumption of ketoconazole (J02AB02) and triazoles (J02AC) for systemic use in ambulatory care between 2010 and 2016. A decline ($P < 0.05$) was noticed in the average annual consumption from 1.455 DID in 2010 to 1.250 DID in 2016, driven by itraconazole ($P < 0.05$). The annual mean consumption of azoles in ambulatory care was 1.357 DID. Fluconazole and itraconazole were the most delivered azole drugs in primary health care as they accounted for 96.4% of the total azoles. According to specialty, the major part (66.1%) of azoles prescriptions were done by general practitioners, with an annual average of 0.898 DID. The second most common prescriptions (13.5% of all azole consumption, 0.184 DID) were done by dermatologists, who notably prescribed 25.0% of all itraconazoles (0.152 DID) consumed in primary health care. Ten per cent of azoles were provided by gynaecologists (0.138 DID) of which the major part was to female patients (98.7%). The remaining prescriptions (10.2%) were carried out by other specialists and dentists (0.138 DID). The cost per inhabitant decreased by 28.5% throughout the study period. For the Belgian social security system, this cost decreased from € 2.00 in 2010 to € 1.43 in 2016 while for the patients, on average it decreased from € 0.35 in 2010 to € 0.25 in 2016 (Figure 4).

3.5 | Overall azole consumption: both hospitals and primary health care

The total annual consumption of systemic azoles (J02AB and J02AC) in Belgium decreased from 1.556 DID in 2010 to 1.330 DID in 2016 ($P < 0.05$), driven by the decrease in itraconazole in ambulatory care. The total fluconazole consumption in Belgium remained relatively stable between 2010 and 2016 with an annual average of 0.776 DID.

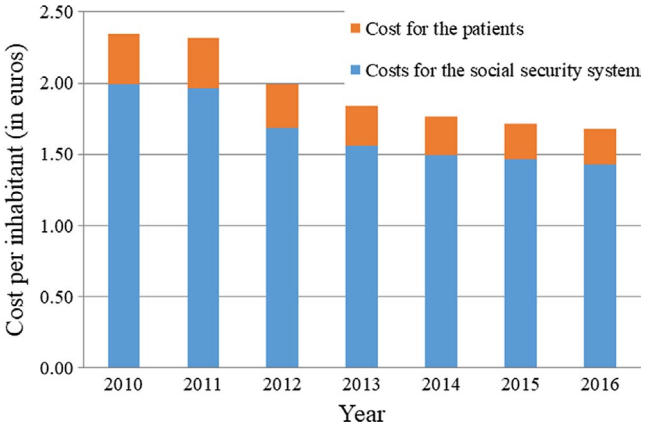

FIGURE 4 Annual costs of systemic azoles (J02AB and J02AC) for the social security system and for the patients prescribed in the ambulatory care sector during 2010-2016

Consequently, its relative proportion to the total consumption increased from 49.0% in 2010 to 57.2% in 2016. Figure 5 shows the differences in systemic azole consumption between hospital and ambulatory care sectors during 2010-2016. The consumption of fluconazole and itraconazole was respectively nine and 175 times higher in the primary healthcare sector than in the hospital care sector. In contrast, there were respectively 18.2% and 37.7% more prescriptions of voriconazole and posaconazole in hospitals compared to primary health care. The oral formulation of ketoconazole was only prescribed to a minor level in both sectors and is not used anymore in Belgium since 2014.

4 | DISCUSSION

Despite the high use of systemic antifungals, especially of fluconazole, consumption decreased in the Belgian hospitals and in the primary healthcare sector. The latter is in agreement with the current situation in most European countries where fluconazole remained the most prescribed systemic antifungal agent and a decreasing trend is observed in the antifungal consumption in

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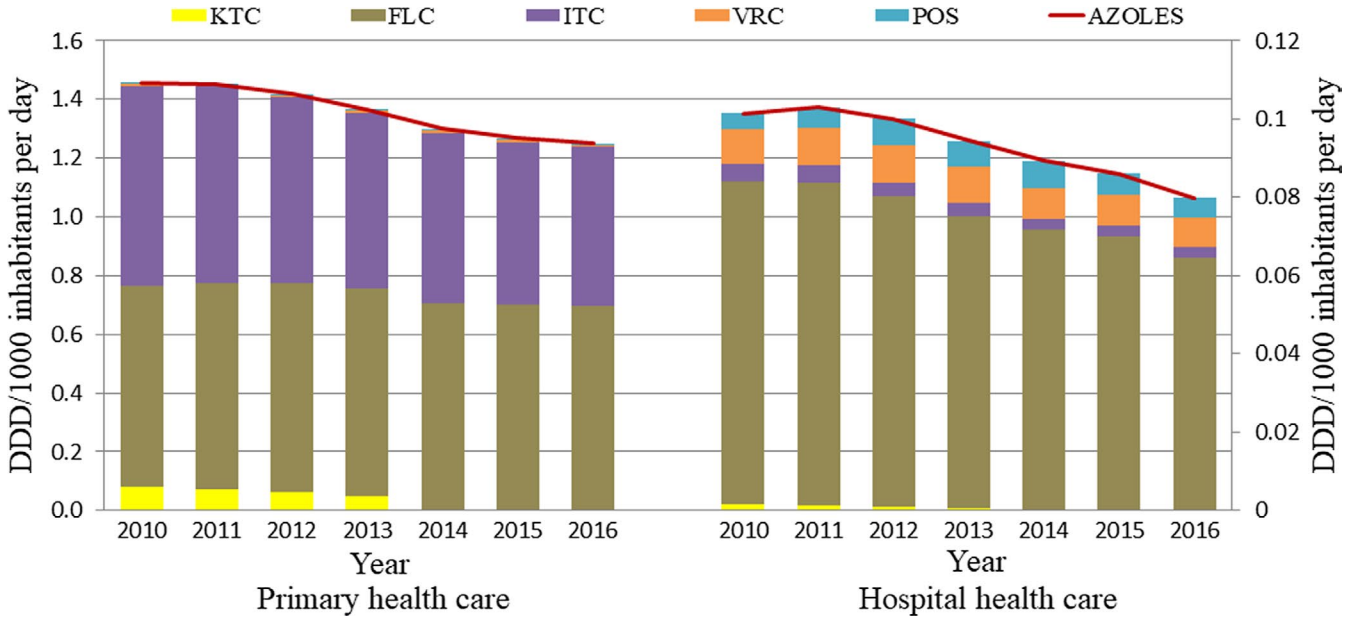

FIGURE 5 Annual average consumption of systemic azoles (J02AB and J02AC) in the hospital sector and the ambulatory care sector during 2010-2016. DDD, defined daily doses; FLC, fluconazole; ITC, itraconazole; KTC, ketoconazole; POS, posaconazole; VRC, voriconazole

both sectors.[6,21-23] According to the European Centre for Disease Prevention and Control (ECDC) antimicrobial consumption database, Belgium had the highest overall fluconazole use within Europe after Greece in 2016 and doubled the European mean.[23]

4.1 | National inpatient data: hospital-wide consumption

The annual average hospital consumption of all systemic antifungal agents decreased over the 14-year study period, and this resulted only from a decrease in non-university hospitals. The epidemiology of invasive nosocomial fungal infections varies by type of patient. The pattern of antifungal consumption can therefore vary according to the teaching level of the hospital under consideration.[7]

The utilisation of fluconazole remained high in Belgian hospitals as it was responsible for almost three-quarters of the total consumption of systemic antifungals. ECDC ranked Belgium together with Italy at the third place for fluconazole consumption in the hospital sector in 2016, after Slovakia and Cyprus.[23] Despite the availability of new antifungal substances (caspofungin, posaconazole and anidulafungin were introduced on the Belgian market in 2001, 2005 and 2007, respectively), fluconazole remained thus largely applied, notably as a treatment of choice for local and invasive *Candida* infections, as well as for prophylaxis in immunocompromised patients.

Regarding echinocandins, the higher consumption of caspofungin compared to anidulafungin is due to its earlier introduction on the Belgian market but also to its broader application. Both echinocandins are indeed used to treat patients with invasive candidiasis but caspofungin is also applied as empirical treatment in febrile neutropenic patients and as salvage treatment in patients with invasive aspergillosis. The echinocandins constitute only a minor part of the total use of systemic antifungals in Belgium. The latter can be attributed to the highly restrictive reimbursement conditions in Belgium and the requirement of an "a priori control" of the advising physician. This is relatively unique in Europe, and consequently, it is not possible to apply the ESCMID guidelines[24-27] on all patients in Belgium. The low consumption of echinocandins in Belgium could also explain the relatively low degree of echinocandin resistance in *Candida* spp. in Belgian hospitals[11,28] in contrast notably to Denmark where it emerged between 2004 and 2015 following an increase in echinocandin consumption.[21]

The additional indication of amphotericin B for the empirical treatment of patients (incl. children) with febrile neutropenia in the haematology-oncology settings in 2010 is suggested to explain the concomitant rise in lipid formulations of this agent. Furthermore, the current DDD of amphotericin B is 35 mg, still referring to the conventional form. Therefore, the quality of the analyses could be improved in the future if separate ATC codes for conventional and lipid amphotericin B formulations would be provided by the WHO.

The non-linear pharmacokinetic profile of voriconazole in adult patients and the wide intra- and interpatient variability makes dosing challenging. Consequently, the variable rate of voriconazole consumption over the years can be explained by the need to optimise therapeutic levels by dose modification as it happens for almost every Belgian patient treated with voriconazole.

4.2 | National inpatient data: consumption per department

In agreement with other studies, the antifungal consumption in ICUs and internal medicine is more elevated than in other units, notably due to the high incidence of candidaemia in both units.[15,29]

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Moreover, ICUs at university hospitals prescribed over 1.5 times more antifungal drugs as compared to ICUs at non-university hospitals. The latter can partly be attributed to the use of antifungal drugs in at-risk transplant patients and other immunocompromised patients, present mainly in ICUs of Belgian university hospitals. As in Germany, ICUs treating these patients have a high antifungal consumption and a multicentre study from Belgium indicated a correlation between the number of transplantations per hospital and the incidence of candidaemia.[15,29] Despite the high antifungal use in ICUs, a decline was observed in the consumption over the 14-year period, mainly driven by fluconazole. A similar trend was observed in a surveillance study at five German university hospitals between 2008 and 2011 and in a Spanish multicentre prospective study performed between 2006 and 2010.[3,28] Internal medicine includes the haematology-oncology where fluconazole is the antimicrobial agent most often prescribed in Belgian university hospitals.[24] Moreover, systemic antifungal agents (J02) account for about one-quarter and one-third of the total antimicrobial use (J01 antibacterials and J02 antifungals) in haematology-oncology units of non-university and university hospitals, respectively.[19]

The relative high use of posaconazole in internal medicine can be attributed to its application as prophylaxis in high-risk patients including neutropenic patients with acute myeloid leukaemia/myelodysplastic syndrome and those with graft-versus-host disease after a haematopoietic stem cell transplantation, both hospitalised at haematology-oncology units.

Burn centres and infectious diseases units were not analysed in details because in number (six and one, respectively) they were very limited in Belgium. A high consumption of antifungals was however observed as these patients are at risk for fungal infections.

4.3 | National outpatient data

In ambulatory care, fluconazole and itraconazole are notably applied for the treatment of candidiasis (thrush and vaginal infections) as well as for some onychomycosis and dermatophytosis.[30]Consumption of voriconazole and posaconazole in ambulatory health care is limited as the later are mainly used in hospitals notably for the treatment of aspergillosis. The Belgian primary healthcare sector is one of the biggest consumers of systemic antifungals (J02) in Europe with a consumption reaching 2.2 times the European mean in 2016.[23,31-36] Almost 95% of all azoles consumed in Belgium are prescribed in primary health care, of which fluconazole and itraconazole account for more than 96%. The decreasing trend in antifungal consumption in ambulatory care is due to itraconazole while fluconazole remains stable, both similar to our neighbouring countries the Netherlands and Luxembourg.[23] Compared to the consumption of systemic azoles (J02AB and J02AC) between 2012 and 2016, the associated social security and average individual patient costs decreased relatively more rapidly. This can be explained by the implementation of the 2012 law (Royal Decree 17/02/2012) obligating doctors and pharmacists to prescribe and deliver the cheapest alternative for a given antimicrobial drug, provided that the molecule, dosage and formulation are identical and that packaging is similar.

4.4 | Strengths and limitations of our study

The major strength of our study is the availability of data on the systemic antifungal use in both hospital and ambulatory healthcare sectors in Belgium. Data for the hospital sector were available over a long time period (14 years) while consumption records of azoles in ambulatory care were collected for the period 2010-2016. Expressions of consumption were available in units of measurement facilitating comparisons with other countries. Surveillance studies reporting antifungal consumption on a national scale can be applied as benchmarking data for other countries, Belgian data being available via Healthstat.[17]

Our study has also some limitations including the lack of stratification by indication (prophylaxis, empirical, pre-emptive or targeted treatments). Details about the route of administration were also not available, and it was not possible to analyse consumption records for adults and children separately. The distinction between the conventional (with major adverse side effects) and less toxic liposomal forms of amphotericin B in the hospital health sector was also not recorded. Different types of ICUs were grouped together, and thus, no distinction could be made in consumption between surgical and medical ICUs or between ICUs treating transplant patients or not. The consumption data for the haematology-oncology unit were included in the internal medicine and could not be analysed separately.

5 | CONCLUSION

In conclusion, despite the decreased trend in overall antifungal consumption, the amount prescribed remains very high in Belgium compared to other European countries. The declining antifungal consumption in Belgian hospitals is driven by lower fluconazole use—solely observed in non-university hospitals—while itraconazole determines the decreasing trend in primary health care. The discrepancy between university and non-university hospitals needs to be explained by further patient-based stratification.

ACKNOWLEDGMENTS

This study was funded by Sciensano, Brussels, Belgium.

CONFLICTS OF INTEREST

Katrien Lagrou reports personal fees and non-financial support from Pfizer, personal fees from Abbott, personal fees and non-financial support from MSD, personal fees from SMB Laboratories, personal fees and non-financial support from Gilead, personal fees from Roche, outside the submitted work. Isabel Spriet reports grants and personal fees from MSD, grants and personal fees from Pfizer,

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personal fees from Gilead, outside the submitted work. Berdieke Goemaere, Marijke Hendrickx, Eline Vandael, Pierre Becker and Boudewijn Catry: none to declare.

AUTHOR CONTRIBUTIONS

B. Goemaere, P. Becker and K. Lagrou conceived the ideas; P. Becker, E. Vandael and B. Catry collected the data; B. Goemaere, P. Becker and E. Vandael analysed the data; B. Goemaere, P. Becker, K. Lagrou contributed to the writing, and B. Catry, I. Spriet, M. Hendrickx and E. Vandael critically revised the writing.

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REFERENCES

1. Banerjee SN, Emori TG, Culver DH, et al. Secular trends in nosocomial primary bloodstream infections in the United States, 1980–1989. *Am J Med*. 1991;91:S86-S89.
2. Pfaller MA, Diekema DJ. Epidemiology of invasive candidiasis: a persistent public health problem. *Clin Microbiol Rev*. 2007;20:133-163.
3. Gross BN, Steib-Bauert M, Kern WV, et al. Hospital use of systemic antifungal drugs: a multi-center surveillance update from Germany. *Infection*. 2015;43:423-429.
4. Hamdy RF, Zaoutis TE, Seo SK. Antifungal stewardship considerations for adults and pediatrics. *Virulence*. 2017;8:658-672.
5. de With K, Steib-Bauert M, Knoth H, et al. Hospital use of systemic antifungal drugs. *BMC Clin Pharmacol*. 2005;5:1.
6. Valerio M, Rodriguez-Gonzalez CG, Muñoz P, et al. Evaluation of antifungal use in a tertiary care institution: antifungal stewardship urgently needed. *J Antimicrob Chemother*. 2014;69:1993-1999.
7. Zarb P, Amadeo B, Muller A, et al. Antifungal therapy in European hospitals: data from the ESAC point-prevalence surveys 2008 and 2009. *Clin Microbiol Infect*. 2012;18:E389-E395.
8. Chow JK, Golan Y, Ruthazer R, et al. Factors associated with candidemia caused by non-albicans *Candida* species versus *Candida albicans* in the intensive care unit. *Clin Infect Dis*. 2008;46:1206-1213.
9. Fournier P, Schwebel C, Maubon D, et al. Antifungal use influences *Candida* species distribution and susceptibility in the intensive care unit. *J Antimicrob Chemother*. 2011;66:2880-2886.
10. Lortholary O, Desnos-Ollivier M, Sitbon K, et al. Recent exposure to caspofungin or fluconazole influences the epidemiology of candidemia: a prospective multicenter study involving 2,441 patients. *Antimicrob Agents Chemother*. 2011;55:532-538.
11. Goemaere B, Becker P, Van Wijngaerden E, et al. Increasing candidaemia incidence from 2004 to 2015 with a shift in epidemiology in patients preexposed to antifungals. *Mycoses*. 2018;61:127-133.
12. Goemaere B, Lagrou K, Spriet I, Hendrickx M, Becker P. Clonal spread in *Candida glabrata* bloodstream isolates and fluconazole resistance affected by prolonged exposure: a 12-year single-center study in Belgium. *Antimicrob Agents Chemother*. 2018; 62: pii: e00591-18.
13. Miller RA. A case for antifungal stewardship. *Curr Fungal Infect Rep*. 2018;12:33-43.
14. Fondevilla E, Grau S, Mojal S, et al. Consumption of systemic antifungal agents among acute care hospitals in Catalonia (Spain), 2008–2013. *Expert Rev Anti Infect Ther*. 2015;14:137-144.
15. Meyer E, Schwab F, Gastmeier P, Ruden H, Heininger A. Antifungal use in intensive care units. *J Antimicrob Chemother*. 2007;60:619-624.
16. Asmundsdottir LR, Erlendsdottir H, Gottfredsson M. Nationwide study of candidemia, antifungal use, and antifungal drug resistance in Iceland, 2000 to 2011. *J Clin Microbiol*. 2013;51:841-848.
17. PROTOCOL Belgian Hospitals. Surveillance of Antimicrobial Consumption (BeH-SAC), 2018, version 1.1. http://www.nsih.be/surv_gm/download_nl.asp. Accessed October 5, 2018.
18. WHO Collaborating Centre for Drug Statistics Methodology. *Guidelines for ATC classification and DDD assignment 2018*. Oslo, Norway: WHO Collaborating Centre for Drug Statistics Methodology, 2017.
19. Ingenbleek A, Van Gastel E, Costers M, Goossens M, Catry B, Magerman K. National report on Consumption of Systemic Antimicrobial Agents in Belgian Hospitals. Scientific Institute of Public Health. 2015; D/2015/2505/57. https://www.sciensano.be/en/biblio/national-report-consumption-systemic-antimicrobial-agents-belgian-hospitals-2007-2013. Accessed October 5, 2018.
20. STATBEL. België in cijfers. Structuur van de bevolking. https://statbel.fgov.be/. Accessed October 5, 2018.
21. Astvad KMT, Johansen HK, Røder BL, et al. Update from a 12-year nationwide fungemia surveillance: increasing intrinsic and acquired resistance causes concern. *J Clin Microbiol*. 2018; 56: pii: e01564-17. https://doi.org/10.1128/jcm.01564
22. Hesstvedt L, Arendrup MC, Poikonen E, et al. Differences in epidemiology of candidaemia in the Nordic countries–what is to blame? *Mycoses*. 2017;60:11-19.
23. European Centre for Disease Prevention and Control. Antimicrobial consumption database, country overview of antimicrobial consumption. https://ecdc.europa.eu/en/antimicrobial-consumption/database/country-overview. Accessed October 5, 2018.
24. Cornely O, Bassetti M, Calandra T, et al. ESCMID guideline for the diagnosis and management of *Candida* diseases 2012: non-neutropenic adult patients. *Clin Microbiol Infect*. 2012;18:19-37.
25. Hope W, Castagnola E, Groll A, et al. ESCMID guideline for the diagnosis and management of *Candida* diseases 2012: prevention and management of invasive infections in neonates and children caused by *Candida* spp. *Clin Microbiol Infect*. 2012;18:38-52.
26. Ullmann A, Akova M, Herbrecht R, et al. ESCMID guideline for the diagnosis and management of *Candida* diseases 2012: adults with haematological malignancies and after haematopoietic stem cell transplantation (HCT). *Clin Microbiol Infect*. 2012;18:53-67.
27. Lortholary O, Petrikkos G, Akova M, et al. ESCMID guideline for the diagnosis and management of *Candida* diseases 2012: patients with HIV infection or AIDS. *Clin Microbiol Infect*. 2012;18:68-77.
28. Olaechea-Astigarraga PM, Alvarez-Lerma F, Palomar-Martínez M, et al. Trends in systemic antifungal use in critically ill patients. Multicenter observational study, 2006-2010. *Enferm Infecc Microbiol Clin*. 2012; 30: 435-440.
29. Trouvé C, Blot S, Hayette MP, et al. Epidemiology and reporting of candidaemia in Belgium: a multi-centre study. *Eur J Clin Microbiol Infect Dis*. 2017;36:649-655.
30. BAPCOC (Belgian Antibiotic Policy Coordination Committee). Belgische gids voor anti-infectieuze behandeling in de ambulante praktijk editie, 2012. https://upb-avb.be/assets/antibioticagids-NL-d96b19ad.pdf. Accessed October 5, 2018.
31. Adriaenssens N, Coenen S, Muller A, et al. European Surveillance of Antimicrobial Consumption (ESAC): outpatient systemic antimycotic and antifungal use in Europe. *J Antimicrob Chemother*. 2010;65:769-774.
32. Adriaenssens N, Coenen S, Versporten A, Goossens H. Outpatient systemic antimycotic and antifungal use in Europe: new outcome measure provides new insight. *Int J Antimicrob Agents*. 2013;42:466-470.
33. Adriaenssens N, Uka V, Versporten A, et al. Systemic antimycotic and antifungal use in eastern Europe: a cross-national database study in coordination with the WHO Regional Office for Europe. *J Antimicrob Chemother*. 2015;70:2173-2175.

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34. European Centre for Disease Prevention and Control. Surveillance of antimicrobial consumption in Europe, 2010. Stockholm: ECDC; 2013. https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/antimicrobial-antibiotic-consumption-ESAC-report-2010-data.pdf. Accessed October 5, 2018.
35. European Centre for Disease Prevention and Control. Surveillance of antimicrobial consumption in Europe 2011. Stockholm: ECDC; 2014. https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/antimicrobial-consumption-europe-surveillance-2011.pdf. Accessed October 5, 2018.
36. European Centre for Disease Prevention and Control. Surveillance of antimicrobial consumption in Europe 2012. Stockholm: ECDC; 2014. https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/antimicrobial-consumption-europe-esac-net-2012.pdf. Accessed October 5, 2018.

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How to cite this article: Goemaere B, Lagrou K, Spriet I, et al. Systemic antifungal drug use in Belgium—One of the biggest antifungal consumers in Europe. *Mycoses*. 2019;62:542–550. https://doi.org/10.1111/myc.12912

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