REVISTA ESPAÑOLA DE Quimioterapia

SOCIEDAD ESPAÑOLA DE QUIMIOTERAPIA

Original

Trends in antifungal use characteristics in primary care in Spain, 2019 to 2024: a nationwide study

Evolución de las características del uso de antifúngicos en atención primaria en España, 2019-2024: un estudio nacional

Álvaro Solaz-García[1,2,a], Héctor Sánchez-Herrero[3,a], Nerea Valles-Murcia[1,2], María José Soriano-Ortega[4], Alba Ruiz-Gaitán[1,5,*]

[1]Hospital Universitari i Politècnic La Fe, Valencia, Spain

[2]Research Group in Perinatology, Health Research Institute Hospital La Fe (IIS La Fe), Valencia, Spain

[3]Research Group in Nursing and Health Care, Instituto de Investigación Sanitaria Puerta de Hierro-Segovia de Arana (IDIPHISA), Majadahonda, Madrid, Spain

[4]Scientific Area, Health Research Institute Hospital La Fe (IIS La Fe), Valencia, Spain

[5]Translational Research on Emerging Pathogens, Microorganisms and Public Health, Severe Infection Research Group, Health Research Institute Hospital La Fe (IIS La Fe), Valencia, Spain

[a]These authors contributed equally to this work and share first authorship

Received: March 20, 2026

Accepted: May 08, 2026

Published: May 29, 2026

***Correspondence:** Alba Ruiz-Gaitán. alba.ruiz@ext.uv.es

Abstract

Background: Antifungal resistance is a growing global concern in the context of antimicrobial resistance. Although primary care is the main setting for managing superficial fungal infections, national evidence on antifungal consumption in Spain remains limited. This study analyzes the characteristics of antifungal use in Spanish primary care.

Methods: A retrospective observational study was conducted using data from the Primary Care Clinical Database of the Spanish Ministry of Health. The study included individuals assigned to primary care with at least one antifungal dispensation per year between 2019-2024. Consumption was measured as Defined Daily Doses (DDD) per 1,000 inhabitants per day (DHD), following the WHO ATC/DDD methodology. Trends were analyzed by sex, age, municipality size, income level, country of birth, and employment status, using annual percentage change (APC) estimated through joinpoint regression models.

Results: From 2019 to 2024, antifungal DHD in Spanish primary care increased significantly overall (APC: 8.4% [6.2-10.5]; p<0.001 for both sexes); the number of individuals with ≥1 dispensation declined in 2020 and then stabilized (APC: 5.3% [2.0-8.6]; p=0.004). Use was consistently higher in women, especially among pensioners (with a widening gap after 2020), unemployed individuals, those with very low income, and those born in Spain; D01A led consumption. Significant APC values were observed across all age, country of birth, employment, municipality size, and income strata, with the largest increases in active workers, small and medium municipalities, males <15 years, and foreign-born.

Conclusions: Systematic monitoring of antifungal consumption in primary care is key to anticipating shifts in epidemiology and guiding antifungal stewardship. This study provides the first nationwide assessment of outpatient antifungal use in Spain from 2019 to 2024, offering critical evidence for public health planning and antimicrobial resistance mitigation.

Keywords: Antifungal agents. Primary care. Epidemiology. Spain. Drug utilization.

Rev Esp Quimioter 2026; 39(3): 253-265

http://www.doi.org/10.37201/req/173.2026

www.revespquimioterapia.com

© 2026 The authors. This article is distributed under the terms of the **Creative Commons Attribution–NonCommercial 4.0 International license (CC BY-NC 4.0)**. Published with index on behalf of Sociedad Española de Quimioterapia.

Resumen

Antecedentes: La resistencia a antifúngicos es una preocupación global creciente en las resistencias antimicrobianas. Aunque la atención primaria gestiona la mayoría de infecciones fúngicas superficiales, la evidencia sobre el uso de antifúngicos en España es limitada. Este estudio analiza las características del uso de antifúngicos en atención primaria.

Métodos: Estudio observacional retrospectivo con datos de la Base de Datos Clínicos de Atención Primaria del Ministerio de Sanidad. Se incluyeron individuos asignados a atención primaria con ≥1 dispensación anual de antifúngicos entre 2019 y 2024. Uso medido en dosis diarias definidas (DDD) por 1.000 habitantes/día (DHD) según la metodología ATC/DDD de la OMS. Tendencias analizadas por sexo, edad, tamaño municipal, nivel de renta, país de nacimiento y situación laboral, mediante el cambio porcentual anual (APC) mediante modelos de regresión joinpoint.

Resultados: Los DHD de antifúngicos en atención primaria aumentaron significativamente en ambos sexos (APC: 8,4% [6,2-10,5]; p<0,001) en 2019-2024; el número de individuos con ≥1 dispensación disminuyó en 2020 y se estabilizó posteriormente (APC: 5,3% [2,0-8,6]; p=0,004). Uso mayor en mujeres, especialmente pensionistas (aumentando la diferencia post-2020), personas desempleadas, personas con ingresos muy bajos y personas nacidas en España; D01A lideró el consumo. Se observaron APC significativos en todos los grupos de edad, país de nacimiento, situación laboral, tamaño municipal e ingresos, con mayores incrementos en trabajadores activos, municipios pequeños y medianos, varones <15 años y personas nacidas en el extranjero.

Conclusiones: Vigilar el consumo de antifúngicos en atención primaria es clave para anticipar cambios epidemiológicos y guiar el uso racional de antifúngicos. Este estudio proporciona la primera evaluación nacional del uso de antifúngicos en atención primaria en España (2019-2024).

Palabras clave: Antifúngicos. Atención primaria. Epidemiología. España. Uso de fármacos.

Introduction

Antimicrobial resistance (AMR) constitutes a major global health emergency, driven primarily by inappropriate and/or excessive antimicrobial use across human, animal, and environmental sectors [1–3]. To address this threat, the European Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections (EU-JAMRAI) has promoted coordinated strategies for surveillance, prevention, and the rational use of antimicrobials following from a One Health perspective [4]. In Spain, the National Plan against Antibiotic Resistance (PRAN) has contributed to measurable reductions in antibiotic consumption, especially in outpatient settings, by promoting evidence-based prescribing and monitoring [5].

Although most attention has traditionally focused on antibiotic consumption, the epidemiology of antifungal use has gained increasing relevance, given the rising global burden of fungal diseases and the emergence of antifungal resistance. In Spain, as in other European countries, over 94% of outpatient antifungal prescriptions correspond to systemic agents such as terbinafine, fluconazole, itraconazole, and ketoconazole [6,7]. Primary care prescriptions target superficial mycoses, including dermatophytosis and mucocutaneous candidiasis, whereas invasive fungal infections are rarely managed at this level [8]. Although resistance rates in community isolates remain comparatively low, recent surveillance studies show a growing prevalence of fluconazole-resistant *Candida* spp., particularly in hospital settings where antifungal exposure and selective pressure are more intense [9–11]. Furthermore, the sharp decline in ketoconazole prescriptions following regulatory restrictions due to hepatotoxicity highlights the impact of pharmacovigilance measures on clinical practice [12].

The upward trend in antifungal consumption parallels patterns long observed for other antimicrobials, particularly antibiotics, which have increased over time in the general population, especially among older adults, and are influenced by sociodemographic and clinical factors including age, sex, educational level, hospitalisation and polypharmacy [13,14]. Although antibiotic use has stabilised or declined in some regions due to stewardship efforts [15,16], antifungal consumption continues to rise in several European countries. By contrast, antiviral use remains lower and restricted to specific indications, with no comparable increase. Meanwhile, hospital-based prescribing of other systemic antifungal classes, such as echinocandins and polyenes, has grown in response to changes in the epidemiology and complexity of invasive fungal infections [17,18].

The rising consumption of antifungal agents carries significant clinical and public health implications. Excessive or inappropriate use, particularly of azoles and echinocandins, promotes the selection of resistant fungal strains through mechanisms such as efflux pump overexpression, target gene mutations, alterations in ergosterol biosynthesis and biofilm formation, all of which compromise therapeutic efficacy [19–24]. Increasing azole resistance has been documented globally and is associated with treatment failure, persistent infection and higher mortality, especially in cases of invasive fungal disease [19–21]. Increased

and sometimes inappropriate use of antifungals in both clinical and agricultural settings has driven the emergence and spread of antifungal-resistant pathogens, such as azole-resistant *Aspergillus fumigatus* and multidrug-resistant *Candidozyma auris* (formerly *Candida auris*), which significantly complicate management and increase mortality [21,22,25–27]. Environmental exposure to agricultural fungicides further contributes to the selection of resistant strains that may later cause human infection, reinforcing the One Health dimension of antifungal resistance [21,25,26]. The limited number of antifungal drug classes means that resistance to one or more agents can severely restrict therapeutic options, sometimes leaving no effective treatments available [19,28]. Overuse and misuse of antifungals also contribute to higher healthcare costs, increased toxicity, and unnecessary medication exposure, highlighting the need for antifungal stewardship programs to optimize use and mitigate resistance [29,30]. These trends underscore the need for antifungal stewardship and robust surveillance systems to safeguard the effectiveness of currently available treatments [19,21,22].

Additionally, environmental contamination with antifungal agents, particularly azoles, has been detected in surface waters and sediments, raising concerns about ecological toxicity and the further selection of resistant strains in the environment, which can subsequently affect human health [21,25,27,31]. The One Health approach, integrating human, animal, and environmental health strategies, is increasingly recognized as essential to address these interconnected clinical, environmental, and agricultural drivers of antifungal resistance [21,27].

Given the growing clinical relevance of fungal infections and the increasing threat of antifungal resistance, characterising outpatient antifungal consumption is crucial. Primary care plays a key role in the management of superficial mycoses and represents the main entry point for antifungal exposure in the general population. However, contemporary nationwide data on antifungal use in Spain's primary care system are lacking.

This study aims to analyse trends in antifungal use in primary care in Spain from 2019 to 2024, quantify consumption patterns using standardised indicators, and explore sociodemographic determinants and temporal changes using data from the Primary Care Clinical Database (BDCAP) of the Ministry of Health.

Methods

Study design. A retrospective observational study was conducted to analyse the use of antifungal agents among individuals with an individual health card assigned to primary care in Spain between 2019 and 2024. The study examined the number of antifungal prescriptions issued in primary care and dispensed in community pharmacies, as well as antifungal consumption expressed as defined daily doses (DDD) per 1,000 persons/day (DHD), following WHO ATC/DDD standards.

Data source. Data were obtained from the *Primary Care Clinical Database* (Base de Datos Clínicos de Atención Primaria, BDCAP) of the Spanish Ministry of Health [32]. This database annually compiles coded and standardised clinical information from primary care for statistical, administrative and research purposes. It was designed to capture clinical activity in a homogeneous and systematic way, with a longitudinal structure derived from electronic health records.

BDCAP is representative of the population with an individual health card assigned to primary care in Spain. For each autonomous community, an independent probabilistic sample was designed using single-stage random cluster sampling based on Basic Health Zones (HBZ), stratified by autonomous community and municipality size. Sampling weights were applied to guarantee representativeness at both regional and national levels. The database includes information on health problems, consultations, comorbidities, procedures, selected laboratory parameters, primary care visits, and prescriptions issued in this setting and dispensed in community pharmacies. This sampling design ensures the robustness of the estimates and allows valid inferences for the entire primary care population.

Study population. Individuals were included if they were assigned to primary care within the Spanish National Health System and had received at least one antifungal prescription issued in primary care and subsequently dispensed in a community pharmacy during the period 2019–2024, the most recent comparable years available in the database. All data were fully anonymised.

Classification of antifungal agents. Antifungal use was classified according to the Anatomical Therapeutic Chemical (ATC) classification system of the World Health Organization (WHO). The following ATC codes were analyzed: A01A (stomatological preparations), A07A (intestinal anti-infectives), D01A (antifungals for topical use), D01B (systemic antifungals for dermatological use), G01A (topical anti-infectives and antiseptics for gynecological use), and J02A (antimycotics for systemic use).

Data were presented as the annual number of individuals with at least one dispensed antifungal prescription and the annual consumption rate expressed

as DHD, which estimates how many of every 1,000 people receive one DDD per day.

Use indicators. The standard DDD, recommended by the WHO for drug-utilisation studies, is defined as the assumed average maintenance dose per day for adults for a drug's main indication and route of administration. DDD values were calculated using the following formula: DDD = amount of active principle consumed / Standard DDD provided by the WHO [33]. Data were expressed as DDD per 1,000 inhabitants per day (DHD), calculated as: DHD = DDD × 1,000 inhabitants / total population × time (days).

Variables and stratification. Analyses were stratified according to the sociodemographic variables available in BDCAP: sex, age group, municipality size, area-level income (when available), country of birth and employment status. Annual indicators comprised the number of individuals with at least one antifungal dispensing, total DDD, annual DHD and the distribution of systemic and topical antifungal use, as well as the contribution of the main active substances.

Statistical analysis. A descriptive analysis was performed to summarise population characteristics using means or medians, with corresponding measures of variability for continuous variables, and frequencies and percentages for categorical variables. Annual rates of antifungal users per 1,000 inhabitants were estimated for each study year.

Temporal trends in antifungal use between 2019 and 2024 were assessed using joinpoint regression models to estimate the annual percentage change (APC) and identify possible changes in slope over time. Interaction terms were included to compare trends across subgroups, and rate ratios with 95% confidence intervals (CI) were estimated. Statistical significance was set at a two-sided $p < 0.05$.

Statistical analyses were performed using Stata 18 and the Joinpoint Regression Program, version 5.4.0 from the National Cancer Institute.

Ethics statement. The study was approved by the Ethics Committee for Research on Medicines of La Fe University and Polytechnic Hospital, Valencia, Spain (Reference: 2024/03/20).

Results

Sociodemographic characteristics of antifungal use in primary care in Spain

Antifungal use in primary care in Spain, measured in DHD, showed an overall increase from 2019 to 2024, with an upward trend after the COVID-19 pandemic. However, the number of individuals with at least one annual dispensation declined in 2020 and subsequently stabilized in the last two years following the post-2020 increase. The D01A group led antifungal use, both in DHD and in the number of individuals, throughout the entire study period (**Supplementary Figure 1**).

Antifungal use in primary care was higher in women than in men across all years of the study period. This difference was particularly marked in individuals aged 65 years and older. Regarding municipality size, women showed higher antifungal use throughout the study period, with greater use in municipalities with fewer than 10,000 inhabitants and in those with 100,001-500,000 inhabitants (**Supplementary Table 1**).

A similar pattern was observed by annual income, with the highest antifungal use among women with very low annual incomes, whereas men and women with incomes above €100,000/year showed similar levels of use (**Supplementary Table 1**).

Women born in Spain showed higher antifungal use than men, as did women born abroad, although the latter had lower antifungal use than Spanish-born women across all years (**Supplementary Table 1**).

According to employment status, the largest differences between women and men were recorded in the unemployed group, where women's antifungal use was nearly double that of men throughout the study period. However, pensioners showed the highest antifungal use overall, with the gender gap widening after 2020 (**Supplementary Table 1**).

Trend analysis

The trend in antifungal DHD increased in parallel and statistically significant for both women and men ($p<0.001$), with an annual increase of 8.4% (6.2-10.5). Similarly, the number of individuals receiving antifungal prescriptions increased significantly in parallel, with an annual increase of 5.3% (2.0-8.6) ($p=0.004$) (**Figure 1**).

A significant increase in antifungal use was observed among men across all age groups. Individuals aged ≥65 years showed the highest use, although with the smallest annual percentage change (APC: 5.7 [2.2-9.3]; $p=0.002$). Conversely, those under 15 years showed the largest increase (APC: 13.9 [7.3-20.5]; $p<0.001$) despite having the lowest primary care use. The pattern of antifungal use by age groups in women was similar to that observed in men, although with a smaller APC in those under 15 years (10.8 [6.2-15.4]; $p<0.001$) and 15-34 years (8.9 [5.3-12.4]; $p<0.001$), and a larger APC in those over 64 years (6.6 [4.4-8.7]; $p<0.001$) (**Figure 2**).

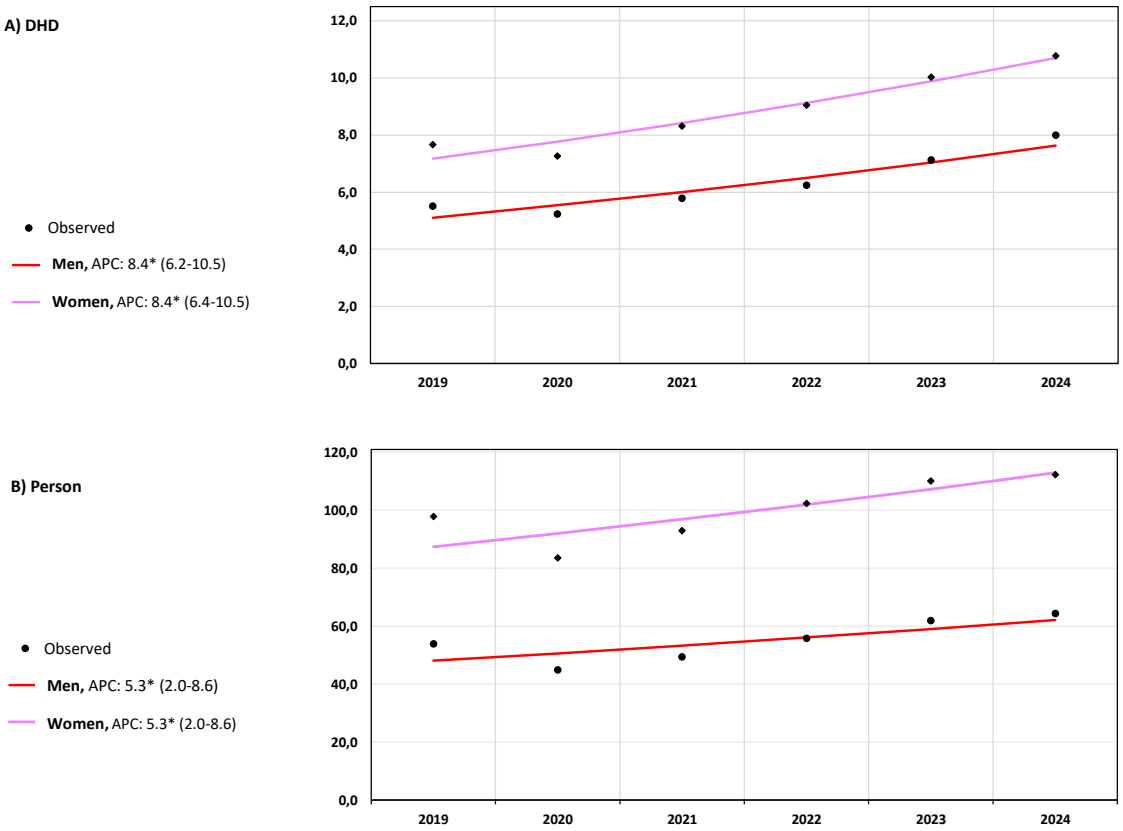

Figure 1. Antifungal use by sex in primary care in Spain (DHD and individuals), 2019-2024

*Statistically significant change in trend (p<0.05)

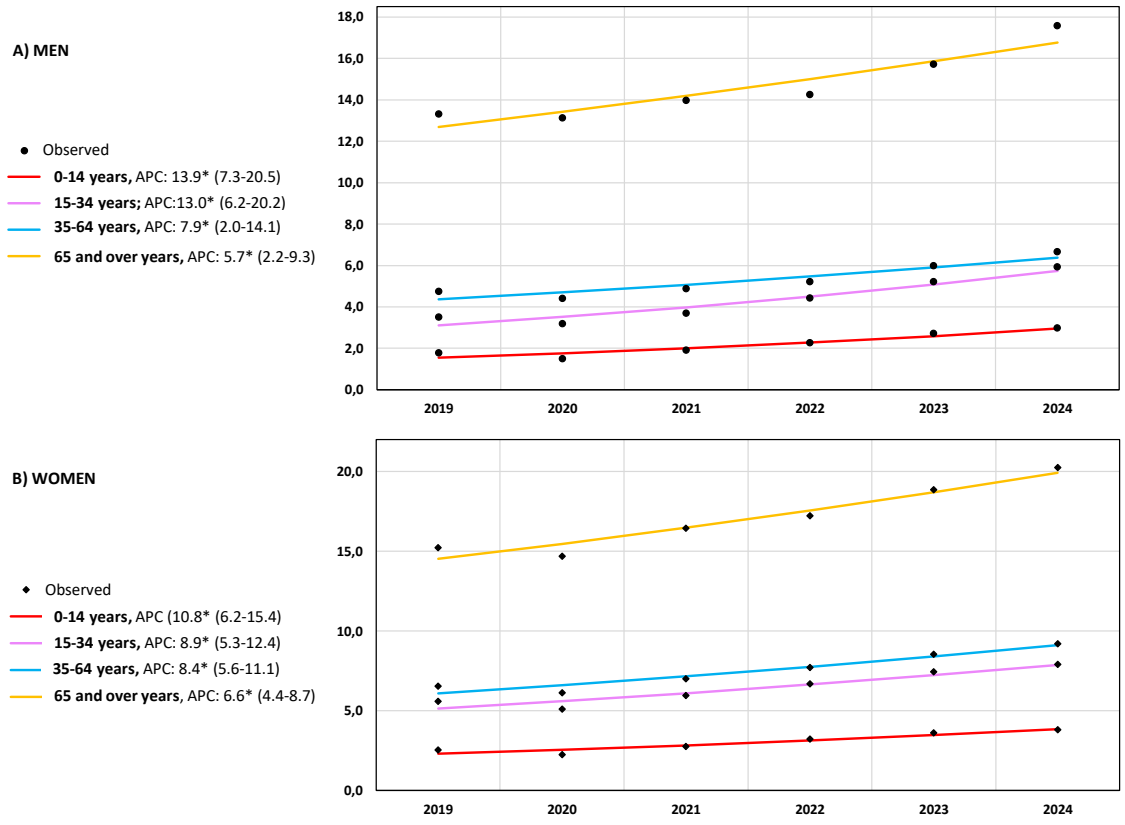

Figure 2. Antifungal use in primary care in Spain by sex and age group (DHD), 2019-2024

*Statistically significant change in trend (p<0.05)

Both men born in Spain and those born abroad showed statistically significant increases in antifungal use, with a greater increase among those born abroad (APC: 9.9 [5.8-14.0]; p<0.001) than among those born in Spain (APC: 9.0 [4.5-13.6]; p<0.001). Women also showed statistically significant increases, with a greater annual increase among those born abroad (APC: 9.8 [5.6-13.9]; p<0.001) than among those born in Spain, whose antifungal use increased by 8.5% (6.1-10.9; p<0.001) (**Figure 3**).

The evolution of antifungal use showed a significantly greater increase among individuals in active employment, both in men (APC: 10.7 [2.4-19.7]; p= 0.012) and women (APC: 8.5 [3.5-13.6]; p<0.001). Conversely, unemployed men showed no statistically significant annual percentage increase (APC: 5.7 [-0.1-12.0]; p=0.054), unlike pensioners (APC: 5.8 [2.6-9.0]; p<0.001). Among unemployed women, the APC was 4.7% ([2.2-7.1]; p<0.001), and it was 7.0% ([5.4-8.5]; p<0.001) among female pensioners (**Figure 4**).

Antifungal use in primary care showed statistically significant increases across all municipality size groups for both men and women. Among men, those living in municipalities of 10,001-50,000 inhabitants showed the largest annual percentage increase (9.5 [4.7-14.4]; p<0.001), followed by those in municipalities of 50,001-100,000 inhabitants with an APC of 9.1% ([3.6-14.9]; p=0.001), whereas those in municipalities of over 500,000 inhabitants showed the smallest increase (APC: 6.9 [0.2-14.0]; p=0.045). In women, the largest annual percentage increase was observed in municipalities of 50,001-100,000 inhabitants (9.3 [5.4-13.4]; p<0.001), while the smallest increase was observed in municipalities with fewer than 10,000 inhabitants (6.9 [4.5-9.3]; p<0.001) (**Figure 5**).

Men with very low annual income levels showed the largest statistically significant increase in antifungal use (APC: 10.8 [5.0-16.8]; p<0.001), followed by those with annual incomes between €18,000 and €99,999, with an annual percentage increase of 8.9% (2.0-16.2; p=0.009). No statistically significant increase was observed among men with annual incomes below €18,000 (p=0.268) or above €100,000 (p=0.064). Women showed statistically significant increase in antifungal use in the very low-income group (6.7% [4.3-9.2]; p<0.001) and among those with annual incomes between €18,000 and €99,999 (9.2% [2.8-16.0]; p=0.004), while the annual percentage increase in the highest income group was 11.6% (2.5-21.7; p<0.013) (**Figure 6**).

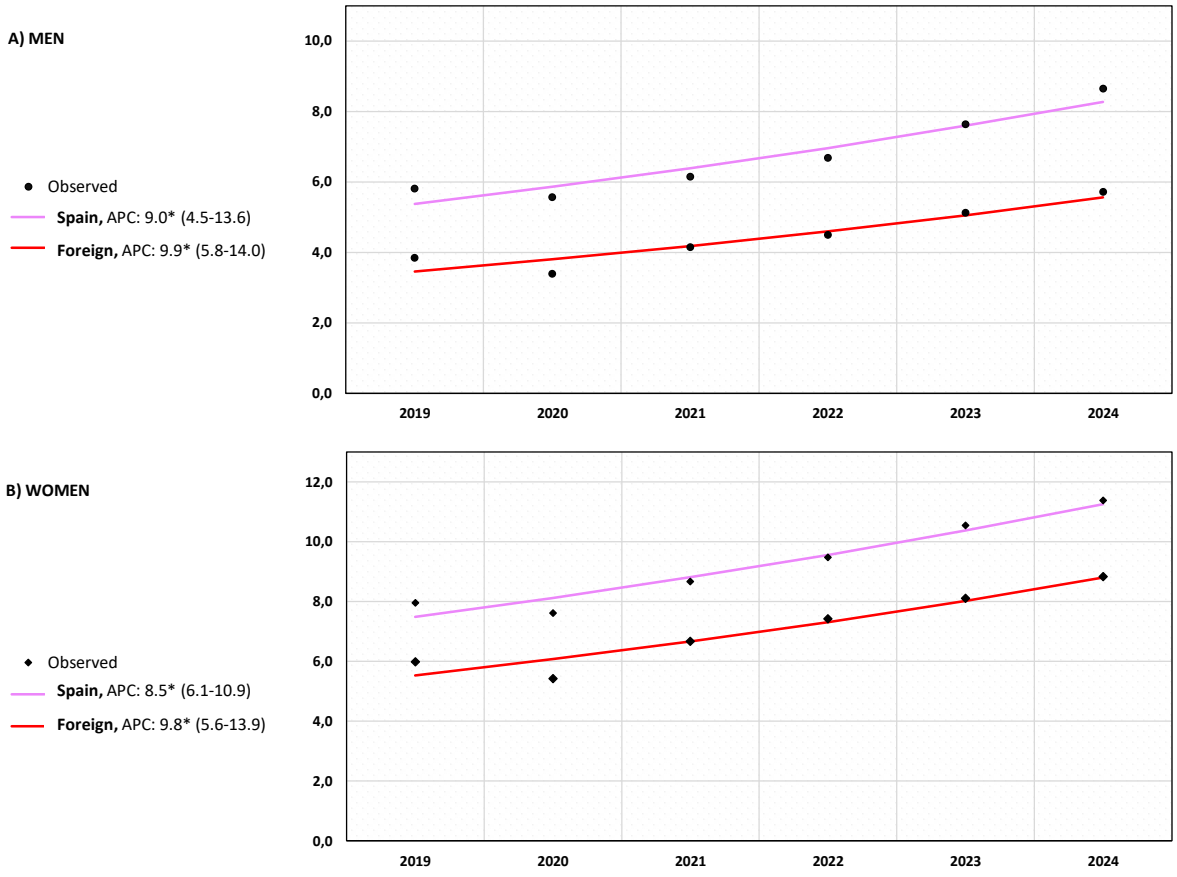

Figure 3. Antifungal use in primary care in Spain by sex and country of birth (DHD), 2019-2024

*Statistically significant change in trend (p<0.05)

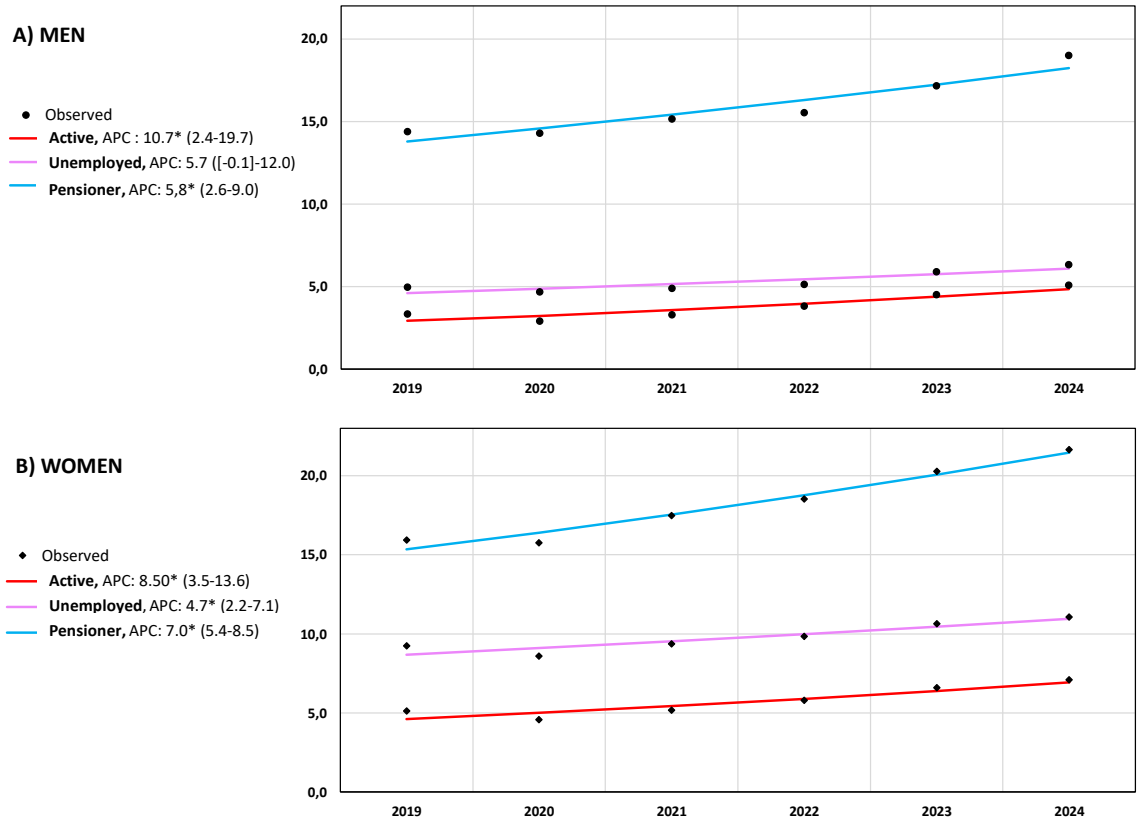

Figure 4. Antifungal use in primary care in Spain by sex and employment status (DHD), 2019-2024

*Statistically significant change in trend (p<0.05)

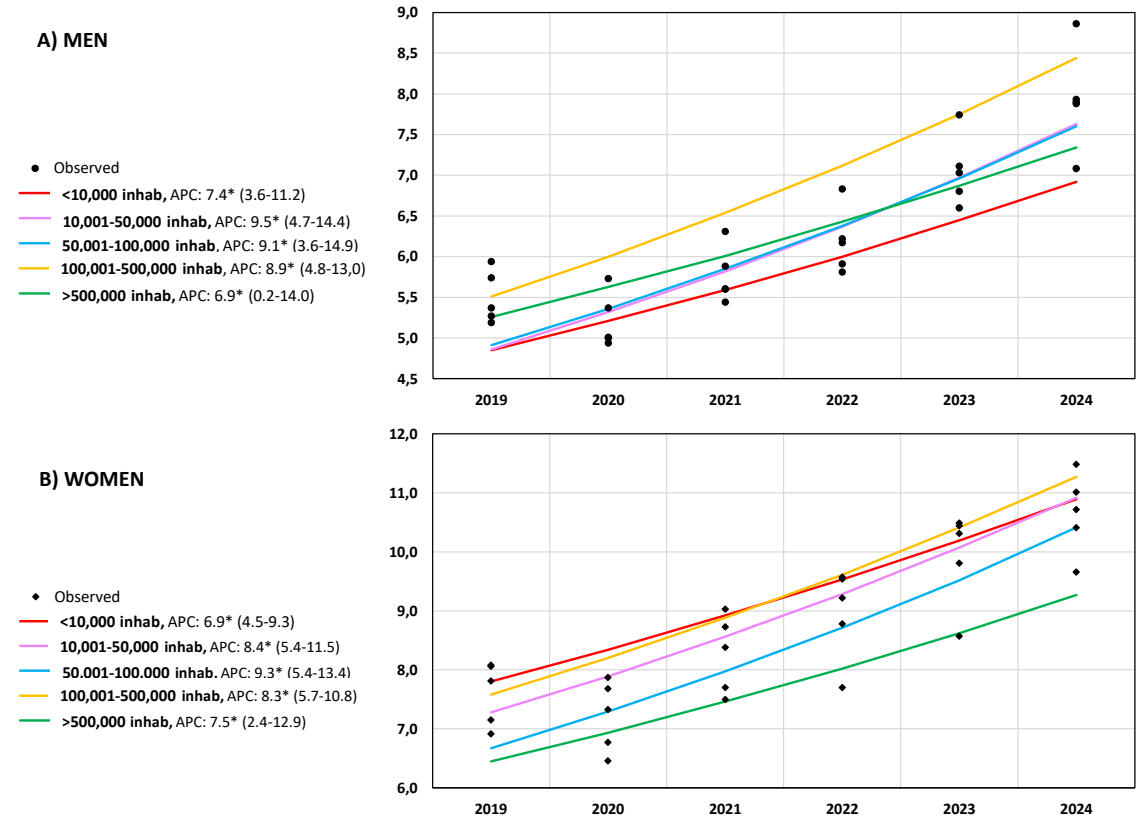

Figure 5. Antifungal use in primary care in Spain by sex and municipality size (DHD), 2019-2024

*Statistically significant change in trend (p<0.05)

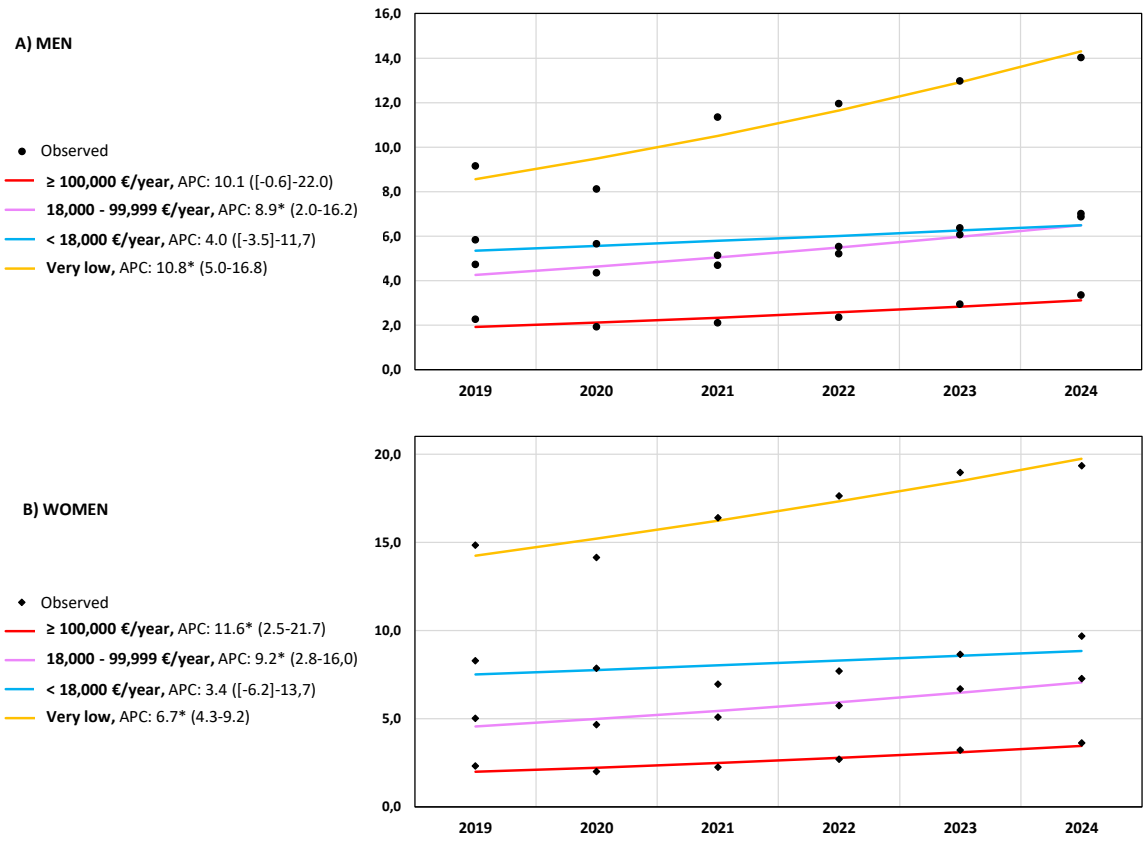

Figure 6. Antifungal use in primary care in Spain by sex and income level (DHD), 2019-2024

*Statistically significant change in trend (p<0.05)

Discussion

This nationwide study provides a comprehensive overview of antifungal use in primary care in Spain between 2019 and 2024 and reveals several relevant epidemiological and public health patterns. First, we observed a sustained overall increase in antifungal consumption measured in DHD, with a transient decrease in 2020 followed by recovery and subsequent growth in the post-COVID period. Notably, the number of individuals receiving at least one annual prescription remained relatively stable in recent years, suggesting that the increase in DHD is driven primarily by greater treatment intensity or longer treatment duration, rather than by an expansion of the treated population. This pattern raises important questions regarding prescribing practices, treatment duration, and potential overuse in community settings.

The predominance of the D01A group, which includes clotrimazole, miconazole, terbinafine, ciclopirox, and nystatin, throughout the study period indicates that topical antifungals remain the principal contributors to total consumption. Although topical antifungals are often perceived as having limited systemic impact, their high and sustained use raises concerns about cumulative selective pressure at mucocutaneous sites and the potential ecological impact of widespread exposure, warranting further evaluation within antifungal stewardship frameworks.

The COVID-19 pandemic had a strong impact on access to primary care, affecting prescription patterns and medication use during 2020 [14]. However, after the first waves of the pandemic in 2020, a recovery was observed in overall medication use and also in antifungals in other countries and contexts [14,34]. This sustained increase may have been influenced by greater empirical prescribing or the recurrence of fungal infections, as well as by possible diagnostic delays as a consequence of the first waves of the COVID-19 pandemic [35].

One of the most consistent findings was the systematically higher antifungal use among women across all years and sociodemographic strata. These differences likely reflect a combination of biological, clinical, and sociocultural factors. Vulvovaginal candidiasis and recurrent mucocutaneous infections are inherently more frequent in women, contributing to higher prescription rates. These results are consistent with previous studies showing that *Candida* infection is one of the most frequent infections among women attending primary care, particularly in the form of vulvovaginitis, which likely explains part of this higher antifungal consumption [36–38].

Additionally, *Candida albicans* has been the species most frequently identified in studies of recurrent vulvovaginitis [39]. Gender differences in healthcare-seeking behavior and diagnostic practices may also influence prescribing patterns.

However, the progressive narrowing of the gender gap in larger municipalities and higher-income strata suggests that structural determinants—such as healthcare access, prescribing culture, and health literacy—may modulate these differences. The wider gap observed in small municipalities and lower-income groups could reflect differential access to specialist care, variations in empirical prescribing, or social vulnerability factors influencing exposure and treatment patterns.

Particularly noteworthy is the temporal increase observed among women born outside Spain, despite their lower absolute use. This may indicate improved access to care, changing epidemiological patterns, or evolving health-seeking behaviors among migrant populations. These findings underscore the importance of incorporating gender- and equity-sensitive approaches into antifungal stewardship initiatives.

Age-related patterns and life-cycle dynamics

Age-stratified analyses revealed distinct and clinically relevant patterns. Absolute consumption was highest among individuals aged ≥65 years, with a particularly marked increase over time. This trend may be explained by multimorbidity, immunosenescence, polypharmacy, diabetes prevalence, and increased contact with healthcare services in older adults. Age-related changes in immune function and higher exposure to invasive procedures may also increase the risk of fungal infection. Polypharmacy and age-related organ dysfunction increase the risk of drug-drug interactions and adverse effects with antifungal agents, particularly azoles, necessitating careful selection and monitoring of therapy in older adults. In summary, the observed increase in antifungal consumption among older adults is explained by a convergence of immunosenescence, comorbidities (notably diabetes), polypharmacy, and greater healthcare exposure, all of which heighten both the risk of fungal infection and the complexity of antifungal management in this population [12,40–42].

In contrast, children under 15 years showed the lowest absolute consumption but the highest relative increases, particularly among boys. Although the clinical drivers remain unclear, this trend deserves attention. It may reflect changes in diagnostic labeling, increased recognition of superficial fungal infections, or shifts in prescribing practices. Given the limited antifungal armamentarium and concerns regarding emerging resistance, monitoring pediatric use is particularly important [43–46].

Socioeconomic and contextual gradients

The study demonstrates a clear socioeconomic gradient in antifungal use. Consumption was consistently higher in women across all income levels and municipal sizes, but growth trends were more pronounced in low- and middle-income groups. No significant increases were observed in the highest income strata. Similarly, municipalities of intermediate size (10,000–100,000 inhabitants) exhibited the most marked growth. These patterns may reflect differences in healthcare accessibility, prescribing behavior, environmental exposure, or broader social determinants of health [47]. The larger gender gap in low-income and small-municipality settings may point to structural inequities influencing both disease burden and prescribing practices [48].

Lower overall use among individuals born outside Spain may be related to barriers to healthcare access, differences in healthcare utilization, or demographic composition. However, the rising trend among migrant women suggests convergence over time and highlights the need for culturally adapted stewardship interventions [29].

Clinical and public health implications: responsible use and antifungal resistance

The sustained increase in antifungal use in primary care must be interpreted within the broader context of antifungal resistance. Antifungal agents are essential for the management of invasive fungal infections and have significantly improved survival in high-risk populations [12,19]. However, increasing and sometimes inappropriate use contributes to the emergence of resistant pathogens.

Authors have documented the rapid global expansion of azole-resistant *Aspergillus fumigatus* and multidrug-resistant *Candidozyma auris* [21,22,25–27]. Given the limited number of antifungal drug classes, resistance to a single agent may substantially restrict therapeutic options, and multidrug resistance may leave no effective therapies available [19,28].

From a clinical perspective, antifungal resistance is associated with therapeutic failure, increased morbidity and mortality, and the need for more toxic or less effective alternatives. Resistance mechanisms such as target-site mutations, efflux pump overexpression, and biofilm formation complicate management [19,22,49,50]. From a public health standpoint, resistance is amplified by inappropriate prescribing, insufficient stewardship, and environmental exposure to azole compounds [21,27,31].

In Spain, national antimicrobial strategies such as PRAN have historically focused primarily on antibiotics, with limited explicit inclusion of antifungals, although the new version of the plan proposes the initiation of surveillance for priority fungal pathogens and antifungal resistance [5]. The findings of this study highlight the need to incorporate antifungal agents into national antimicrobial stewardship policies, particularly in primary care, where the majority of prescriptions occur. Community-based antifungal stewardship should include prescriber education, diagnostic support, treatment-duration optimization, and integration of antifungal consumption data with resistance surveillance systems.

A One Health perspective is also essential. Environmental contamination with azoles and the use of agricultural fungicides contribute to the selection of resistant strains that may subsequently infect humans [21,25,27]. Climate change and the emergence of thermotolerant fungi further complicate this landscape. Coordinated surveillance integrating human, veterinary, agricultural, and environmental data is therefore critical.

Strengths and limitations

This study has several strengths. It is nationwide and longitudinal, and includes detailed sociodemographic disaggregation, allowing the identification of vulnerable subgroups and nuanced trend analyses. Standardized DHD measures facilitate comparison with other antimicrobial consumption studies.

However, some limitations must be acknowledged. DHD represents a proxy for consumption and does not capture clinical indication, appropriateness of prescribing, dosage accuracy, adherence, or microbiological confirmation. Resistance data were not available, precluding a direct correlation between use and resistance trends. Additionally, unmeasured confounding factors such as local prescribing culture, diagnostic practices, or changes in clinical guidelines may have influenced the observed patterns.

The data are limited to the ATC groups A01A, A07A, D01A, D01B, G01A, and J02A, with no information on specific antifungal agents. The study is based on sample-based data rather than a population-based registry, potentially leading to under-reporting due to increased physician workload. Non-prescription pharmacy sales were unavailable, as they fall outside the scope of the BDCAP database. However, the quality control procedures and extrapolation methodology used by BDCAP ensure reliable estimates and minimize bias.

Conclusions

In conclusion, antifungal use in Spanish primary care increased steadily between 2019 and 2024, with upward trends observed in both women and men and marked differences across age, municipality size, income level, country of birth, and employment status. The rise in DHD without parallel growth in the number of treated individuals suggests increasing treatment intensity. Given the growing global threat of antifungal resistance and the limited therapeutic arsenal available, these findings underscore the urgent need to incorporate antifungal agents into antimicrobial stewardship frameworks, strengthen community-level surveillance, and adopt a One Health approach to preserve the effectiveness of existing antifungal therapies.

Acknowledgements

We would like to acknowledge the professionals at the Ministry of Health and the autonomous communities who provide the data.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. A.R.G is supported by a Juan Rodés contract (JR21/00061) from the Instituto de Salud Carlos III, co-funded by the European Union.

Author contributions

Conceptualization: A.S.G. and H.S.H.; methodology: H.S.H., A.S.G. and A.R.G.; validation and formal analysis: H.S.H., N.V.M., M.J.S.O., and A.R.G.; writing original draft preparation: H.S.H. and A.S.G.; writing, review and editing: H.S.H., A.S.G., N.V.M., M.J.S.O., and A.R.G. All authors have read and approved the final version of the manuscript.

Conflict of interests

The authors declare that they have no competing interests.

Ethics statements

The study was approved by the Ethics Committee for Research on Medicines of La Fe University and Polytechnic Hospital, Valencia, Spain (Reference: 2024/03/20). As the research used anonymised secondary data from the Primary Care Clinical Database (BDCAP), individual informed consent was not required.

Data availability statement

Data were obtained from the Primary Care Clinical Database (Base de Datos Clínicos de Atención

Primaria, BDCAP) of the Spanish Ministry of Health. This database annually compiles coded and standardised clinical information from primary care for statistical, clinical-administrative, and research purposes. It is designed to systematically capture population-based clinical activity using electronic health records from a longitudinal perspective. Public information about the BDCAP is available on the Ministry of Health website: https://www.sanidad.gob.es/estadEstudios/estadisticas/estadisticas/estMinisterio/SIAP/home.htm.

AI statement

No artificial intelligence tools were used in the writing, analysis, interpretation, or review of this article.

Supplementary material

The supplementary material is available on the website of the Revista Española de Quimioterapia.

References

1. Holmes AH, Moore LSP, Sundsfjord A, Steinbakk M, Regmi S, Karkey A, et al. Understanding the mechanisms and drivers of antimicrobial resistance. Lancet. 2016;387(10014):176-87. Available from: https://doi.org/10.1016/S0140-6736(15)00473-0
2. O'Neill J. Tackling drug-resistant infections globally: final report and recommendations. Review on Antimicrobial Resistance; 2016. Available from: https://amr-review.org/background.html
3. World Health Organization. Global action plan on antimicrobial resistance. Geneva: World Health Organization; 2015 [cited 2026 Mar 3]. Available from: https://www.who.int/publications/i/item/9789241509763
4. European Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections (EU-JAMRAI). Layman report by the EU-JAMRAI. FEMS [Internet]. 2021 [cited 2026 march 3]. Available from: https://fems-microbiology.org/opportunities/layman-report-by-the-eu-jamrai/
5. Spanish Ministry of Health. National Plan against Antibiotic Resistance (PRAN) (PRAN) 2025-2027 [Internet]. Madrid: Ministry of Health; 2025 [cited 2026 march 3]. Available from: https://resistenciaantibioticos.es/es/publicaciones/plan-nacional-frente-la-resistencia-los-antibioticos-pran-2025-2027
6. Adriaenssens N, Coenen S, Muller A, Vankerckhoven V, Goossens H, ESAC Project Group. European Surveillance of Antimicrobial Consumption (ESAC): outpatient systemic antimycotic and antifungal use in Europe. J Antimicrob Chemother. 2010;65(4):769-74. Available from: https://doi.org/10.1093/jac/dkq023
7. 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(5):466-70. Available from: https://doi.org/10.1016/j.ijantimicag.2013.07.004
8. Rodriguez-Tudela JL, Alastruey-Izquierdo A, Gago S, Cuenca-Estrella M, León C, Miro JM, et al. Burden of serious fungal infections in Spain. Clin Microbiol Infect. 2015;21(2):183-9. Available from: https://doi.org/10.1016/j.cmi.2014.07.013
9. Díaz-García J, Machado M, Alcalá L, Reigadas E, Pérez-Ayala A, Gómez-García de la Pedrosa E, et al. Trends in antifungal resistance in Candida from a multicenter study conducted in Madrid (CANDIMAD study): fluconazole-resistant C. parapsilosis spreading has gained traction in 2022. Antimicrob Agents Chemother. 2023;67(11):e0098623. Available from: https://doi.org/10.1128/aac.00986-23
10. Nieto MC, Tellería O, Cisterna R. Sentinel surveillance of invasive candidiasis in Spain: epidemiology and antifungal susceptibility. Diagn Microbiol Infect Dis. 2015;81(1):34-40. Available from: https://doi.org/10.1016/j.diagmicrobio.2014.05.021
11. Guinea J, Zaragoza Ó, Escribano P, Martín-Mazuelos E, Pemán J, Sánchez-Reus F, et al. Molecular identification and antifungal susceptibility of yeast isolates causing fungemia collected in a population-based study in Spain in 2010 and 2011. Antimicrob Agents Chemother. 2014;58(3):1529-37. Available from: https://doi.org/10.1128/AAC.02155-13
12. Pathadka S, Yan VKC, Neoh CF, Al-Badriyeh D, Kong DCM, Slavin MA, et al. Global Consumption Trend of Antifungal Agents in Humans From 2008 to 2018: Data From 65 Middle- and High-Income Countries. Drugs. 2022;82(11):1193-205. Available from: https://doi.org/10.1007/s40265-022-01751-x
13. Palacios-Ceña D, Hernández-Barrera V, Jiménez-Trujillo I, Serrano-Urrea R, Fernández-de-Las-Peñas C, Carrasco-Garrido P. Time trends in antibiotic consumption in the elderly: Ten-year follow-up of the Spanish National Health Survey and the European Health Interview Survey for Spain (2003-2014). PLoS One. 2017;12(11):e0185869. Available from: https://doi.org/10.1371/journal.pone.0185869
14. Sánchez-Herrero H, Solaz-García Á, Pinilla-González A, Martínez-Sánchez EV, Santágueda-Balader P, Cernada-Badía M. Epidemiological characteristics of antimicrobial use in Primary Care in Spain: a nationwide study. Rev Esp Quimioter. 2025;38(2):115-25. Available from: https://doi.org/10.37201/req/120.2024
15. Lázaro Bengoa E, Madurga Sanz M, de Abajo Iglesias FJ. [Trends in antibiotic consumption in Spain, 1985-2000]. Med Clin (Barc). 2002;118(15):561-8. Available from: https://doi.org/10.1016/s0025-7753(02)72453-6
16. Bremón AR, Ruiz-Tovar M, Gorricho BP, de Torres PD, Rodríguez RL. Non-hospital consumption of antibiotics in Spain: 1987-1997. J Antimicrob Chemother. 2000;45(3):395-400. Available from: https://doi.org/10.1093/jac/45.3.395
17. Fondevilla E, Grau S, Mojal S, Palomar M, Matas L, Gudiol F, et al. Consumption of systemic antifungal agents among acute care hospitals in Catalonia (Spain), 2008-2013. Expert Rev Anti Infect Ther. 2016;14(1):137-44. Available from: https://doi.org/10.1586/14787210.2016.1096776
18. Bienvenu AL, Bestion A, Pradat P, Richard JC, Argaud L, Guichon C, et al. Impact of COVID-19 pandemic on antifungal consumption: a multicenter retrospective analysis. Crit Care. 2022;26(1):384. Available from: https://doi.org/10.1186/s13054-022-04270-z
19. Perlin DS, Rautemaa-Richardson R, Alastruey-Izquierdo A. The global problem of antifungal resistance: prevalence, mechanisms, and management. Lancet Infect Dis. 2017;17(12):e383-92. Available from: https://doi.org/10.

1016/S1473-3099(17)30316-X

20. Pristov KE, Ghannoum MA. Resistance of Candida to azoles and echinocandins worldwide. Clin Microbiol Infect. 2019;25(7):792-8. Available from: https://doi.org/10.1016/j.cmi.2019.03.028

21. Fisher MC, Alastruey-Izquierdo A, Berman J, Bicanic T, Bignell EM, Bowyer P, et al. Tackling the emerging threat of antifungal resistance to human health. Nat Rev Microbiol. 2022;20(9):557-71. Available from: https://doi.org/10.1038/s41579-022-00720-1

22. Lockhart SR, Chowdhary A, Gold JAW. The rapid emergence of antifungal-resistant human-pathogenic fungi. Nat Rev Microbiol. 2023;21(12):818-32. Available from: https://doi.org/10.1038/s41579-023-00960-9

23. Dahiya S, Sharma N, Punia A, Choudhary P, Gulia P, Parmar VS, et al. Antimycotic Drugs and their Mechanisms of Resistance to Candida Species. Curr Drug Targets. 2022;23(2):116-25. Available from: https://doi.org/10.2174/1389450122666210719124143

24. Cowen LE, Sanglard D, Howard SJ, Rogers PD, Perlin DS. Mechanisms of Antifungal Drug Resistance. Cold Spring Harb Perspect Med. 2014;5(7):a019752. Available from: https://doi.org/10.1101/cshperspect.a019752

25. Bastos RW, Rossato L, Goldman GH, Santos DA. Fungicide effects on human fungal pathogens: Cross-resistance to medical drugs and beyond. PLoS Pathog. 2021;17(12):e1010073. Available from: https://doi.org/10.1371/journal.ppat.1010073

26. Gow NAR, Johnson C, Berman J, Coste AT, Cuomo CA, Perlin DS, et al. The importance of antimicrobial resistance in medical mycology. Nat Commun. 2022;13(1):5352. Available from: https://doi.org/10.1038/s41467-022-32249-5

27. Williams CC, Gregory JB, Usher J. Understanding the clinical and environmental drivers of antifungal resistance in the One Health context. Microbiology (Reading). 2024;170(10):001512. Available from: https://doi.org/10.1099/mic.0.001512

28. Kriegl L, Egger M, Boyer J, Hoenigl M, Krause R. New treatment options for critically important WHO fungal priority pathogens. Clin Microbiol Infect. 2025;31(6):922-30. Available from: https://doi.org/10.1016/j.cmi.2024.03.006

29. Muñoz P, Valerio M, Vena A, Bouza E. Antifungal stewardship in daily practice and health economic implications. Mycoses. 2015;58(Suppl 2):14-25. Available from: https://doi.org/10.1111/myc.12329

30. Cole DC, Govender NP, Chakrabarti A, Sacarlal J, Denning DW. Improvement of fungal disease identification and management: combined health systems and public health approaches. Lancet Infect Dis. 2017;17(12):e412-9. Available from: https://doi.org/10.1016/S1473-3099(17)30308-0

31. Garvey M, Meade E, Rowan NJ. Effectiveness of front line and emerging fungal disease prevention and control interventions and opportunities to address appropriate eco-sustainable solutions. Sci Total Environ. 2022;851(Pt 2):158284. Available from: https://doi.org/10.1016/j.scitotenv.2022.158284

32. Subdirección General de Información Sanitaria. Ministerio de Sanidad [Internet]. 2014 [cited 2026 march 3]. Base de Datos Clínicos de Atención Primaria (BDCAP). Available from: https://www.sanidad.gob.es/estadEstudios/estadisticas/estadisticas/estMinisterio/SIAP/home.htm

33. WHO Collaborating Centre for Drug Statistics Methodology. ATC classification index with DDDs: Structure and principles [Internet]. 2022 [cited 2026 march 3]. Available from: https://atcddd.fhi.no/atc/structure_and_principles/

34. Cruz SP de la, Cebrino J. Prevalence and Determinants of Antibiotic Consumption in the Elderly during 2006-2017. Int J Environ Res Public Health. 2020;17(9):3243. Available from: https://doi.org/10.3390/ijerph17093243

35. Monika P, Chandraprabha MN. Risks of mucormycosis in the current Covid-19 pandemic: a clinical challenge in both immunocompromised and immunocompetent patients. Mol Biol Rep. 2022;49(6):4977-88. Available from: https://doi.org/10.1007/s11033-022-07160-3

36. Kufa T, Gumede L, Maseko DV, Radebe F, Kularatne R. The demographic and clinical profiles of women presenting with vaginal discharge syndrome at primary care facilities in South Africa: Associations with age and implications for management. S Afr Med J. 2018;108(10):876-80. Available from: https://doi.org/10.7196/SAMJ.2018.v108i10.13027

37. Barry MS, Ba Diallo A, Diadhiou M, Mall I, Gassama O, Ndiaye Guèye MD, et al. Accuracy of syndromic management in targeting vaginal and cervical infections among symptomatic women of reproductive age attending primary care clinics in Dakar, Senegal. Trop Med Int Health. 2018;23(5):541-8. Available from: https://doi.org/10.1111/tmi.13046

38. Khadka S, Khatri R, Chaudhary R. Infective Vaginal Discharge among Women of the Reproductive Age in the Outpatient Department of a Primary Care Centre. JNMA J Nepal Med Assoc. 2024;62(270):103-5. Available from: https://doi.org/10.31729/jnma.8432

39. Cooke G, Watson C, Deckx L, Pirotta M, Smith J, van Driel ML. Treatment for recurrent vulvovaginal candidiasis (thrush). Cochrane Database Syst Rev. 2022;1(1):CD009151. Available from: https://doi.org/10.1002/14651858.CD009151.pub2

40. Pfaller MA, Carvalhaes CG, DeVries S, Huband MD, Castanheira M. Elderly versus nonelderly patients with invasive fungal infections: species distribution and antifungal resistance, SENTRY antifungal surveillance program 2017-2019. Diagn Microbiol Infect Dis. 2022;102(4):115627. Available from: https://doi.org/10.1016/j.diagmicrobio.2021.115627

41. Lewis ED, Wu D, Meydani SN. Age-associated alterations in immune function and inflammation. Prog Neuropsychopharmacol Biol Psychiatry. 2022;118:110576. Available from: https://doi.org/10.1016/j.pnpbp.2022.110576

42. Kauffman CA. Fungal infections in older adults. Clin Infect Dis. 2001;33(4):550-5. Available from: https://doi.org/10.1086/322685

43. Pemán J, Cantón E, Linares-Sicilia MJ, Roselló EM, Borrell N, Ruiz-Pérez-de-Pipaon MT, et al. Epidemiology and antifungal susceptibility of bloodstream fungal isolates in pediatric patients: a Spanish multicenter prospective survey. J Clin Microbiol. 2011;49(12):4158-63. Available from: https://doi.org/10.1128/JCM.05474-11

44. Lestner JM, Versporten A, Doerholt K, Warris A, Roilides E, Sharland M, et al. Systemic antifungal prescribing in neonates and children: outcomes from the Antibiotic

Resistance and Prescribing in European Children (ARPEC) Study. Antimicrob Agents Chemother. 2015;59(2):782-9. Available from: https://doi.org/10.1128/AAC.04109-14

45. Chorafa E, Iosifidis E, Oletto A, Warris A, Castagnola E, Bruggemann R, et al. Antifungal Use in Immunocompromised Children in Europe: A 12-Week Multicenter Weekly Point Prevalence Survey (CALYPSO). J Pediatr Hematol Oncol. 2025;47(6):e222-30. Available from: https://doi.org/10.1097/MPH.0000000000003070

46. Gupta AK, Venkataraman M, Talukder M. Onychomycosis in Older Adults: Prevalence, Diagnosis, and Management. Drugs Aging. 2022;39(3):191-8. Available from: https://doi.org/10.1007/s40266-021-00917-8

47. Kaur R, Kashyap B, Bhalla P. Onychomycosis--epidemiology, diagnosis and management. Indian J Med Microbiol. 2008;26(2):108-16. Available from: https://doi.org/10.4103/0255-0857.40522

48. Shutt AE, Ashiru-Oredope D, Price J, Padoveze MC, Shafiq N, Carter E, et al. The intersection of the social determinants of health and antimicrobial resistance in human populations: a systematic review. BMJ Glob Health. 2025;10(5). Available from: https://doi.org/10.1136/bmjgh-2024-017389

49. Halliday C, Alguacil-Cuéllar L, Chen SCA, Alastruey-Izquierdo A. Optimizing antifungal therapies for Candida infections: evidence, resistance, and emerging approaches. Clin Microbiol Infect. 2026;32(3):365-73. Available from: https://doi.org/10.1016/j.cmi.2025.10.008

50. Van Rhijn N, White PL. Antifungal treatment strategies and their impact on resistance development in clinical settings. J Antimicrob Chemother. 2025;80(12):3208-26. Available from: https://doi.org/10.1093/jac/dkaf382