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Trends in systemic antifungal use in Australia, 2005–2016: a time-series analysis

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Abstract

Data on antifungal utilization trends are important to encourage antifungal stewardship. This study explored the utilization of antifungal agents for systemic use and the impact of reimbursement policy changes in Australia. We analyzed national data from the Australian Pharmaceutical Benefits Scheme (PBS) (2005–2016). We examined patterns of use over time and the impact of reimbursement decisions on antifungal use with an interrupted time-series model. In 2005-2016, there has been an increase in the use of most antifungals, especially fluconazole, itraconazole and posaconazole. Ketoconazole was the most commonly dispensed systemic antifungal (46.0%) before its PBS listing removal, when it was replaced by fluconazole (69.8%). The PBS event "Fluconazole and itraconazole restrictions eased" led to increased use of fluconazole (0.025/1000 per day with no delay). Both the largest rates and numerical increase were among obstetricians and gynecologists (1,969%; 1,851 dispensed prescriptions) and dermatologists (1,723%; 1,689 dispensed prescriptions) except general practitioner (2010-2016). This is the first Australian national longitudinal estimate of systemic antifungal use. It shows an overall increase in prescribing of most antifungals during study period, with reimbursement decisions impacting utilization. These data provide a baseline to inform development of national antifungal guidelines and policies to encourage more targeted antifungal stewardship.

Introduction

The high mortality and diagnostic challenge of invasive fungal infection (IFI) have encouraged the use of broad-spectrum and costly antifungal agents (1). Studies suggest the rate of inappropriate prescribing of antifungals ranges between 25% and 75% (2, 3). Factors contributing to sub-optimal antifungal prescribing include empirical therapy, incorrect interpretation of IFI risks, sometimes poor local diagnostics and inadequate prescriber knowledge of IFI. Inappropriate use of antifungal agents may lead to a variety of adverse consequences including unnecessary medicine exposure, persistent infection, and increased costs and toxicities (4). Furthermore, inappropriate antifungal use has contributed to the global increase in resistance to both triazole and echinocandin antifungal agents; this poses an increasing threat to food security and human health (5, 6). The emergence of drug resistance to any one medicine class severely limits therapy because fewer treatment options are available (7).

Most antimicrobial surveillance has focused on antibacterial treatment, with few studies investigating antifungal use (8). Antibacterials are used more frequently than antifungal agents but, given growing antifungal resistance, a better understanding of antifungal use is needed to guide antifungal stewardship. As there are only a few systemic antifungals available, stewardship is particularly important. A vital first step is to assess the extent of use so that targets can be established for optimal use.

Differences in use might be related to healthcare policies and regulations (9). In Australia, there have been important changes to the listing of antifungals on Australia's national and subsidized formulary – the Pharmaceutical Benefits Schedule (PBS): new listings and delisting of antifungal agents; and new indications for some antifungals. We aimed to describe the dispensed use of antifungal agents in Australia and to identify how PBS reimbursement policy changes affected antifungal use between 2005 and 2016.

Materials and Methods

We examined the use of antifungal medicines for systemic use, dispensed as subsidized medicines in Australia between 2005 and 2016. For the triazole antifungal class (i.e. the most commonly used antifungal class in Australia), the use of dispensed prescriptions over time was compared by prescriber classification (general practitioner (GP) – either vocationally registered as a GP or non-vocationally registered without GP specialist qualifications – and other specialist) and by dose form (consistent with those included in the Australian Medicines Handbook) (10).

Data source

We purchased data from the Department of Human Services (DHS) Medicare (11) for each formulation of each systemic antifungal dispensed on the PBS between January 2005 and September 2016. The PBS is a national formulary that subsidises a comprehensive range of registered medicines to Australian citizens. PBS medicines

are mostly prescribed in the community and do not routinely include medicines prescribed to hospital inpatients (12). These data only include medicines prescribed, dispensed and used in the community setting. There are two levels of copayments – one for general beneficiaries (AU$38.30 in 2016) (13) and a lower one for concessional beneficiaries (those on social security) (AU$6.20 in 2016). Some medicines are priced below the copayment for general beneficiaries (under co-payment, i.e. not PBS-subsidized) and dispensing data for those are collected as well to PBS-subsidized data. The data supplied by DHS included under co-payment dispensed prescriptions from 1 April 2012. We used dispensed data for date of supply so there may be small differences compared with publicly available date of processing data (14).

Antifungal products and listing changes

We calculated dispensed medicine use for medicines in Anatomical Therapeutic Chemical (ATC) codes J02A (antimycotics for systemic use) (15). Antimycotics are broadly classified as: triazoles (fluconazole, itraconazole, posaconazole, voriconazole); imidazoles (ketoconazole, miconazole); antibiotics (amphotericin B); antimetabolites (flucytosine); and echinocandins (anidulafungin, caspofungin, micafungin). We included antifungal agents used to treat invasive fungal infections available on the PBS in Australia (i.e. amphotericin B (excluding liposomal), fluconazole, ketoconazole, itraconazole, posaconazole, voriconazole) and excluded medicines that are only indicated for dermatophyte infections (i.e., griseofulvin and terbinafine).

Many medications on the PBS are subsidised for a specific patient group or indication. There are three restriction categories: 1) Unrestricted benefits (no restrictions apply to their therapeutic use); 2) Restricted benefits (can only be prescribed for specific therapeutic uses); and 3) Authority required benefits (prescriber must gain approval from Services Australia for the prescription to be valid). We analyzed dispensed use of these systematic antifungal agents within the context of six PBS antifungal listing or delisting events: 1) posaconazole and voriconazole were listed on PBS in the first quarter of 2009 (Posaconazole and Voriconazole listed); 2) amphotericin B was discontinued and subsequently deleted from the PBS in the last quarter of 2010 (Amphotericin B delisted); 3) ketoconazole was deregistered and its supply discontinued in Australia on 1 December 2013 due to risk of liver injury (Ketoconazole removed); 4) voriconazole was listed for prophylaxis against invasive fungal infections on 1 December 2014 (Voriconazole listed for prophylaxis); 5) posaconazole tablets were listed on 1 September 2015 with the same restrictions as the oral liquid (Introduction of posaconazole tablet); 6) the listings for fluconazole and itraconazole were changed from Streamlined Authority listings (for specific conditions prescribing is authorized by using a provided four digit authority code) to Restricted Benefit listings (can be prescribed without authority approval if the condition meets the stated restrictions) in April 2016 (Fluconazole and itraconazole restrictions eased, i.e. a less stringent requirement for prescribing).

Utilization unit

We calculated the number of defined daily doses (DDD) per 1,000 people per day (DDD/1,000 per day) for each unique antifungal agent. We obtained the mid-year Australian resident population values from the Department of Social Services annual reports (16). The use of the DDD metric might give misleading results in an analysis by dose formulation since the higher dose products will have higher use values than lower-dose products. Therefore, we used the number of prescriptions when comparing different dose formulations within the same medicine.

Analysis

We examined changes in the use of antifungals over the study period using linear regression methods. We used time series analyses with autoregressive integrated moving average (ARIMA) models using the Box–Jenkins method integrating the stochastic dependence of consecutive data over time (17). After obtaining the univariate ARIMA models, we identified the transfer function model from the cross-correlation function estimating the correlations between the PBS events at different time delays (lags) and antifungal use. The PBS (de)listing events were modelled as an intervention variable coded '1' for the quarters of events existing, and '0' for other quarters during the study period. We then estimated the transfer function model, accounting for possible time delays of up to two quarters (18). We used significance tests for parameter estimates at a *P* value of <0.05 to eliminate the unnecessary terms. All final model residuals passed a 'white noise' test (based on Ljung–Box

statistics). All statistical analyses were performed with SAS 9.4 (SAS Inc).

Results

Overall use

Systemic antifungal use in prescriptions and DDD/1,000 per day supplied on the PBS increased over time for most products (Table 1). PBS changes in reimbursement and (de)listings led to changes in the use of individual antifungals. Amphotericin B prescriptions decreased between 2005 and 2010; this low use is consistent with the drug being deleted from the PBS in 2010. Ketoconazole was PBS delisted and removed from the Australian market in December 2013 but prior to this, it was the most frequently prescribed antifungal agent (46.0%), followed by fluconazole (39.5%) and itraconazole (9.5%). From 2014, fluconazole dominated antifungal use (69.8%), followed by itraconazole (14.3%) and voriconazole (8.2%), with the latter two agents only PBS-listed in 2009 (Figure 1 and Table 2).

Fluconazole increased 0.025/1,000/day and itraconazole increased 0.0040/1,000/day immediately (i.e. no delay) after they were changed from Streamlined Authority to Restricted Benefit listings in April 2016. The other PBS events did not affect the use of antifungals i.e. posaconazole and voriconazole listed, amphotericin B delisted, ketoconazole removed, and the new collection of under co-payment data.

Fluconazole

Fluconazole use increased from 0.047/1,000/day to 0.125/1,000/day over 12 years (Table 1). There was a sudden increase in fluconazole use in the second quarter of 2016 after the listing changed to a (lower) Restricted Benefit (Figure 1). Fluconazole has seven dose formulations: three capsules, three solutions for intravenous (iv) infusion, and one oral suspension. The use of fluconazole capsules increased over time; the 200mg dose was preferred with a higher rate of increased use while the 50 mg dose increased three-fold in 2016 (Figure 2a). The use of fluconazole products for IV administration decreased from 2014 to the second quarter of 2016 when the 200 mg solution for IV infusion increased substantially. The 400 mg solution of IV infusion is infrequently supplied on the PBS. The use of the fluconazole suspension appears to have stabilized in 2014 (Figure 2b).

The use of fluconazole capsules and 200 mg solution of IV infusion in the first to third quarters of 2005, 2010 and 2016 varied by prescriber type. The capsules were most frequently prescribed by GPs followed by hematologists, who also have the largest numerical increase in prescriptions in 2005-2016. When using 2010 and 2016 data for comparison, both the largest rates and numerical increase were among obstetricians and gynecologists (1,969%; 1,851 dispensed prescriptions) and dermatologists (1,723%; 1,689 dispensed prescriptions) except GP (2005-2016; Figure 3a). The 200 mg IV formulation was most commonly prescribed by non-

vocationally registered GPs (most likely in rural settings), physicians, and surgeons. Both the largest rates and numerical increase in dispensed use was also among surgeons (1,243%; 174 dispensed prescriptions) and unclassified GPs (553%; 83 dispensed prescriptions) (Figure 3b).

Itraconazole

Prior to 2011, the number of prescriptions supplied per quarter was relatively stable and has increased steadily since 2011. There have been a small number of 50 mg capsules supplied since they were listed on 1 April 2016.

Posaconazole and voriconazole

The dispensed use of posaconazole increased steadily with a plateau of use between 2012 and 2014 (Figure 4a). PBS listing of the tablet formulation in late 2015 was associated with a dramatic increase in the total dispensed use. After establishing the ARIMA model of the posaconazole oral suspension $((0,1,0)\ (0,1,0)_4)$, a clear drop in the use of oral suspension after the introduction of the tablets was shown (P=0.0002), with a reduction of 210.6 (SE 47.7) prescription immediately (i.e. no delay).

When examining use by dose form, the voriconazole 200 mg tablet remains the most used dose formulation; use peaked in early 2014 and subsequently decreased (Figure 4b). Use of the 50 mg tablet and oral suspension were stable from late 2012 onwards. Voriconazole was listed for prophylaxis against invasive fungal infections on 1

December 2014. The number of prescriptions for prophylaxis increased until December 2015 and decreased thereafter (Figure 4c).

Discussion

This study of Australian national dispensing data showed increasing use of most systemic antifungal agents over 12 years. Ketoconazole was the most commonly administered systemic antifungal before it was delisted and replaced by fluconazole as the most commonly prescribed antifungal. We report increased use of fluconazole and itraconazole after the prescribing restrictions for fluconazole and itraconazole were eased.

There are few systematically reported data on antifungal consumption (8, 19, 20). We observed increasing use of antifungal agents between 2005 and 2016. This finding is consistent with previous reports from Spain and Germany (19, 20) but there was a decline in antifungal use in US national billing data analysis (8), suggesting variations among countries. The increased antifungal use over time may reflect a growing number of immunosuppressed patients in the community; such as those with cancer (the case diagnosed of all blood cancer in Australia was 11,156 in 2005 and 15,722 in 2016 (21)), hematopoietic and solid organ transplants (the number of transplant recipients was increased from 799 in 2009 to 1,447 in 2016 (22)), and cystic fibrosis (the total number of cystic fibrosis was 3,156 in 2012, increasing to 3,422 in 2016 (23)). As these patients are more susceptible to

developing opportunistic fungal infections, including HIV-related infections (24) and candidemia (25), antifungals may be used in high-risk patients in anticipation of a fungal infection.

Ketoconazole was commonly prescribed before it was deregistered but other antifungals did not replace ketoconazole immediately following this policy change. This raises the question why patients with the appropriate indication for ketoconazole did not receive an alternative PBS-listed antifungal. Fluconazole use increased substantially in the second quarter of 2016, likely driven by increased prescribing of the 50 mg and 100 mg oral capsules. This increase occurred only after easing the restriction level (streamlined authority to restricted benefit) with no change in the indications for use.

Except GP, the largest ratios and numerical increase in fluconazole prescriptions was among obstetricians and gynecologists, and dermatologists. This may be due to prescribing for vulvovaginal candidiasis by gynecologists or for dermatophyte infections by dermatologists (26). The largest increase in 200 mg IV solution was due to greater prescribing by surgeons and unclassified GPs. Possible reasons include fluconazole being prescribed by surgeons to prevent intra-abdominal candidiasis in high-risk surgical patients, and by unclassified GPs (working in a rural setting) to prevent or control fungal urinary tract fungal infection, oropharyngeal/oesophageal candidiasis in immunosuppressed and/or neutropenic patients, prevent fungal

peritonitis in peritoneal dialysis, or in neonatal candidaemia. The increasing use of telehealth consulting over the last decade has enabled rural patients to be managed in their local community, with IV fluconazole prescriptions advised by urban-based specialists.

After the posaconazole tablet formulation was introduced, the use of the oral suspension declined substantially and we noted that tablet usage exceeded the use of oral suspension from the second quarter. This may reflect a preference for the tablet, which is not only a more portable dose form but has been reported to produce higher plasma trough concentrations than the oral suspension (12). Decreasing voriconazole use could be due to several factors but, primarily, a clinical preference for posaconazole over voriconazole for prophylaxis in terms of safety (27). The voriconazole PBS listing is limited to patients receiving hematopoietic allogenic stem cell transplantation (AlloHSCT) sourced bone marrow of an unrelated donor or from umbilical cord blood. In 2013, 73% of AlloHSCTs used peripheral blood stem cells and would not be eligible for PBS subsidy (28). Many AlloHSCT patients can probably access posaconazole under existing restrictions and patients receiving autologous or allogenic HSCTs for acute myelocytic leukemia or myelodysplastic syndrome will meet criteria for posaconazole (29). Additionally, posaconazole has a broader spectrum of activity that includes activity neutropenic patients and solid-organ transplantation.

The strength of this study is that it is the first thorough examination of dispensing of antifungals for systemic use in Australia over an extended time period. The longitudinal data provides a useful overview of antifungal use. In addition, by using appropriate statistical methods (i.e. ARIMA and the transfer function model), our study offers further evidence of how health policy changes such as PBS reimbursement events influence use. Our study has three limitations. Firstly, we do not know if the dispensed use reflects actual consumption by an individual patient. The data on use are not linked to any information on patient outcomes. Secondly, the PBS data do not provide information on the reason for the prescription so we cannot determine the indication or type of treatment for these antifungals. Lastly, the data do not allow us to assess the appropriateness of antifungal use. As there is no contemporaneous Australian evidence-based clinical practice resource dedicated to comprehensive guidance on the prevention and management of systemic fungal infections, increases in antifungal use may signal inappropriate use (30, 31). A lack of compliance with national or international guidelines has a negative impact on patient outcomes. In one French study, only 65% of the antifungal agents were prescribed according to international guidelines or labelling, with the overall survival rate at 12 weeks significantly higher in patients receiving appropriate therapy than those receiving inappropriate treatment (2). In a Thai study, the rate of inappropriate antifungal use reached 70% (32). The most serious issue caused by inappropriate antifungal use is antifungal resistance although the risk of resistance is not as high as for antibiotics. Because of rising resistance to fluconazole (33), the 2016 candidiasis

treatment guidelines from the Infectious Diseases Society of America recommend echinocandins as first-line therapy for invasive candidiasis in all adult patient populations (34). However, echinocandins were not registered for use in Australia during the study period. There are no national data on antifungal-resistance. Ongoing monitoring of antifungal use and changes in drug susceptibility is essential.

In conclusion, this study provides the first record of systemic antifungal use in Australia. The use of most systemic antifungal agents increased over 12 years although low overall use compared with antibacterial agents. Some PBS (de)listing events affected antifungal use e.g. a sharp increase in the use of fluconazole after restrictions were eased. Inappropriate prescribing of antifungals can accelerate the development of resistant fungal strains and result in adverse patient outcomes. A better understanding of antifungal use could inform the development of national guidelines and more targeted antifungal stewardship for appropriate antifungal use.

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Conflict of interests

The authors declare that they have no conflict of interests.

Authors' contributions

Concept and design: YW, SH. Acquisition, analysis or interpretation of data: YW, SH, MVD, TM. Drafting of the manuscript: all authors. Critical revision of the manuscript for important intellectual content: all authors. All authors read and approved the final manuscript.

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Figure Legends

Figure 1. Dispensed use (DDD/1000 per day) of systematic antifungal agents between 2005 and 2016. AMB, amphotericin B; FLU, fluconazole; KET, ketoconazole; ITR, itraconazole; POS, posaconazole; VOR, voriconazole.

Figure 2. Fluconazole use (number of prescriptions). a, capsules. b, suspension and IV solution formulations.

Figure 3. Fluconazole use (number of prescriptions) by prescriber specialty (for 2005, 2010 and 2016). a. capsules and b. 200 mg fluconazole IV formulation. GP, general practitioner; VR, vocationally registered.

Figure 4. Posaconazole and voriconazole use (number of prescriptions). a. posaconazole by dose formulation; b. voriconazole by dose formulation; c. voriconazole for the indication of prophylaxis.

Table 1: Use of Total all antifungals in number of prescriptions, proportion of category (%), and use (DDD/1000 per day) for each year 2005-2016

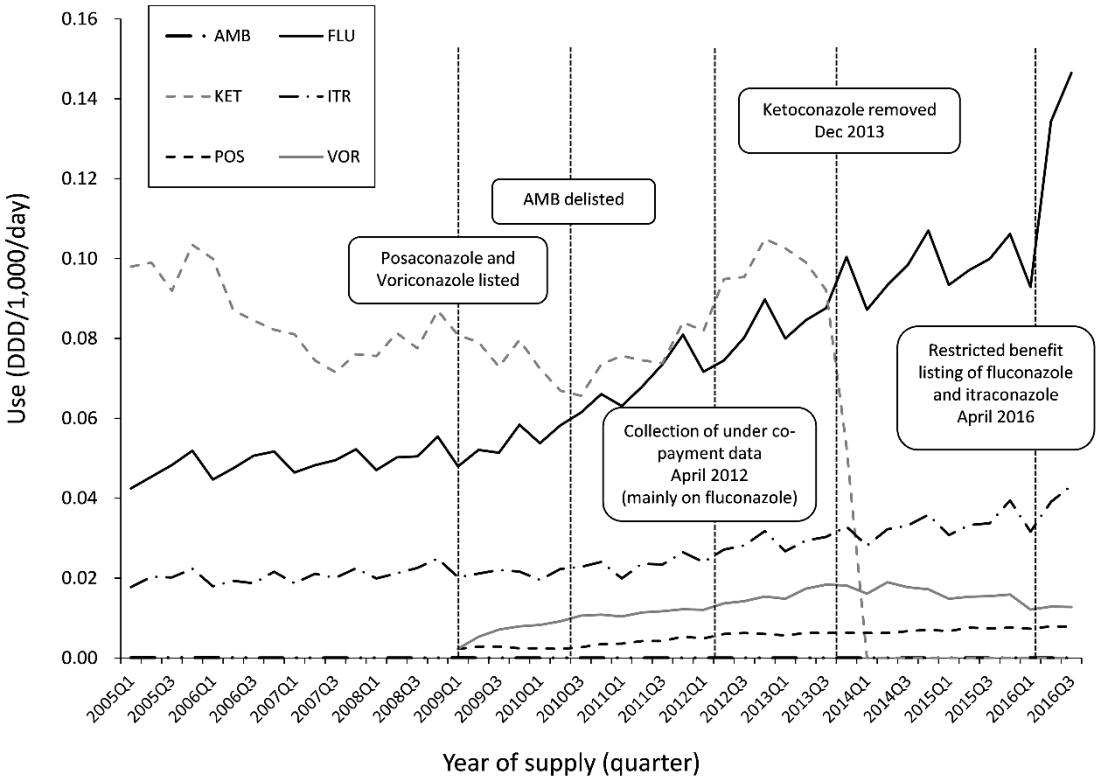
		Amphotericin B			Fluconazole			Ketoconazole			Itraconazole			Voriconazole			Posaconazole		
Year	Total population	Total scripts	%	Use	Total scripts	%	Use	Total scripts	%	Use	Total scripts	%	Use	Total scripts	%	Use	Total scripts	%	Use
2005	20,224,502	281	0.5	0.00005	19,060	34.4	0.047	31,072	56.1	0.098	4,962	9.0	0.020	0	0	0	0	0	0
2006	20,517,802	254	0.5	0.00005	19,992	37.5	0.049	28,291	53.0	0.088	4,844	9.1	0.019	0	0	0	0	0	0
2007	20,894,526	124	0.2	0.00002	20,839	40.9	0.049	24,768	48.6	0.076	5,235	10.3	0.021	0	0	0	0	0	0
2008	21,329,214	109	0.2	0.00002	22,015	40.5	0.051	26,448	48.7	0.080	5,766	10.6	0.022	0	0	0	0	0	0
2009	21,752,666	116	0.2	0.00002	22,928	39.5	0.052	26,084	44.9	0.078	5,627	9.7	0.021	1,834	3.2	0.006	1,480	2.5	0.003
2010	22,080,742	16	0	0.000003	25,308	42.1	0.060	23,959	39.9	0.070	5,963	9.9	0.022	3,304	5.5	0.010	1,564	2.6	0.003
2011	22,407,702	0	0	0	30,165	43.0	0.071	27,127	38.7	0.077	6,374	9.1	0.023	3,959	5.6	0.011	2,549	3.6	0.004
2012	22,818,406	0	0	0	33,815	37.8	0.079	39,379	44.0	0.094	7,740	8.7	0.028	5,008	5.6	0.014	3,465	3.9	0.006
2013	23,202,354	0	0	0	38,139	40.1	0.088	38,543	40.5	0.087	8,426	8.9	0.030	6,344	6.7	0.017	3,709	3.9	0.006
2014	23,558,824	0	0	0	42,727	67.9	0.096	0	0	0	9,281	14.7	0.032	6,550	10.4	0.017	4,401	7.0	0.007
2015	23,902,480	0	0	0	44,565	67.9	0.099	0	0	0	9,986	15.2	0.034	5,982	9.1	0.015	5,062	7.7	0.007
2016	24,220,432	0	0	0	65,561	73.5	0.125	0	0	0	11,636	13.0	0.038	4,495	5.0	0.013	7,503	8.4	0.008

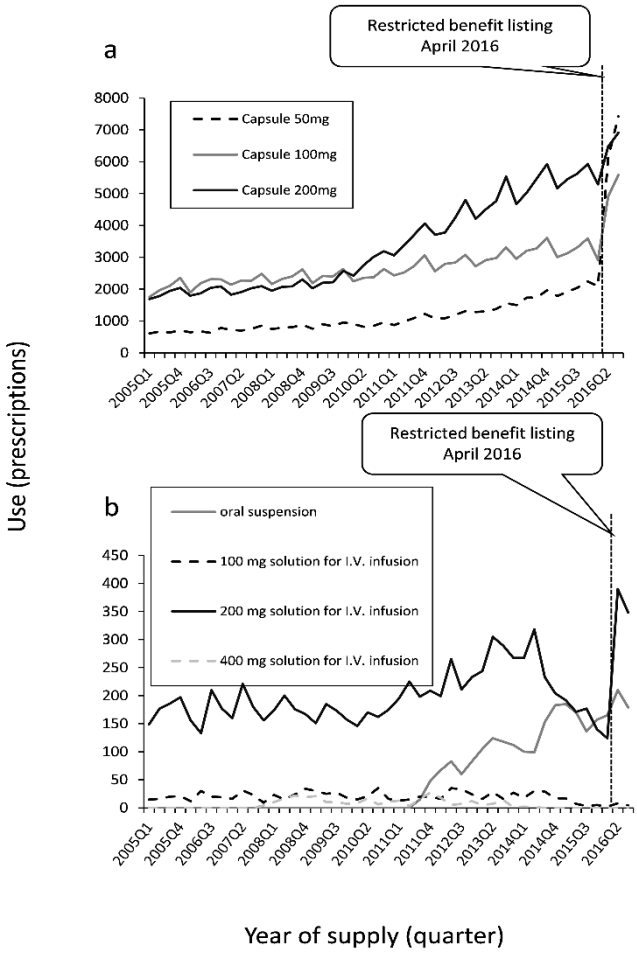
*2016 data corrected for scripts multiplying by the factor 1.3333333 (=4/3) and for DDDs by 274 days instead of 365 days as in 2016 has 3 quarter data

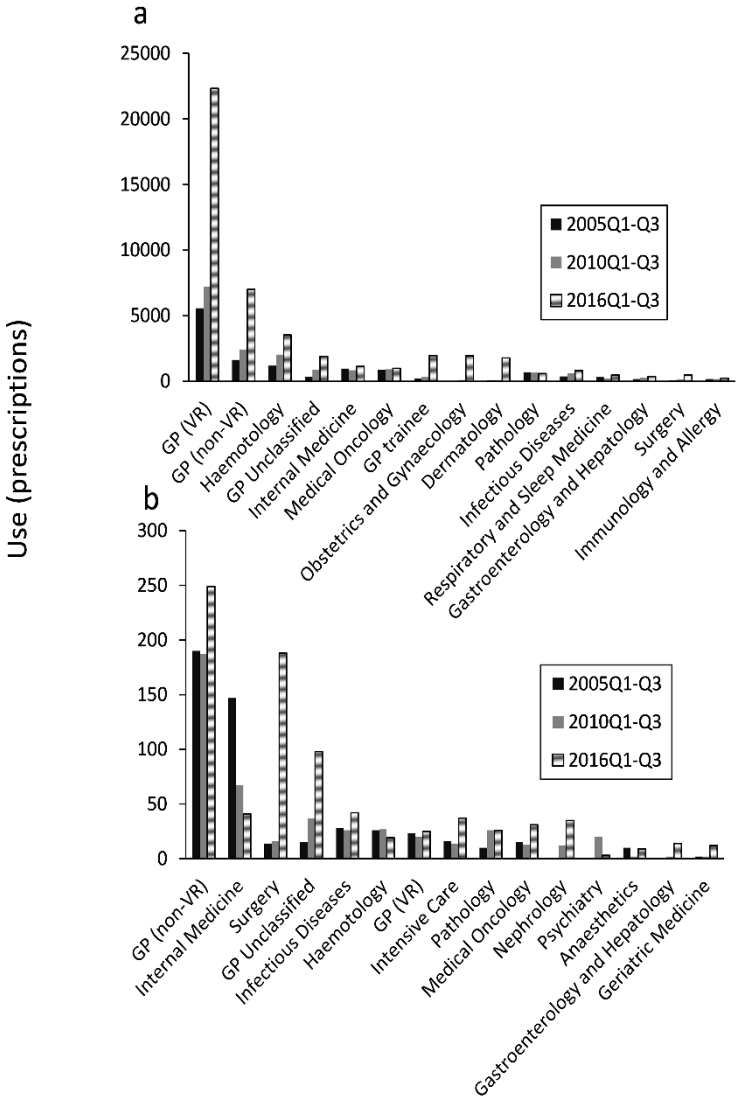
Table 2: The impact of five PBS events on the use of six systemic antifungal agents in Australia (January 2005 to June 2016)

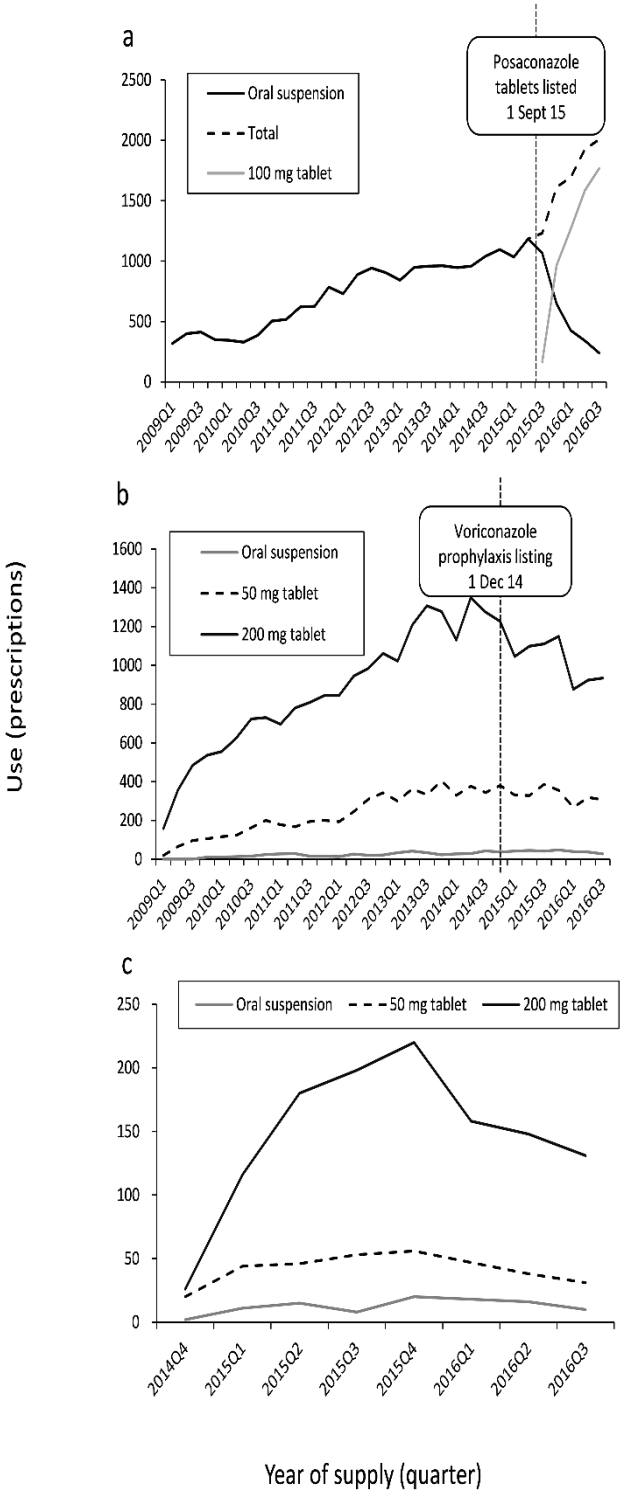
			Posaconazole and Voriconazole listed			Amphotericin B delisted			Collection of under co-payment data			Ketoconazole removed			Fluconazole and itraconazole restrictions eased		
Antifungals	***ARIMA* structure**	**Trend (*P*)**	Lag*	Parameter (SE)	*P*	Lag*	Parameter (SE)	*P*	Lag*	Parameter (SE)	*P*	Lag*	Parameter (SE)	*P*	Lag*	Parameter (SE)	*P*
Amphotericin B	(1,1,0)	Downward (<0.001)	NS	NS	NS	-	-	-	-	-	-	-	-	-	-	-	-
Fluconazole	$(0,1,0)(0,1,0)_4$	Upward (<0.001)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	0	0.025 (0.0021)	<0.001
Ketoconazole	(1,1,0)	No (0.409)	NS	NS	NS	NS	NS	NS	NS	NS	NS	-	-	-	-	-	-
Itraconazole	$(0,1,0)(0,1,1)_4$	Upward (<0.001)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	0	0.0040 (0.0008)	<0.001
Posaconazole	(1,1,0)	Upward (<0.001)	-	-	-	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Voriconazole	$(0,1,0)(0,1,0)_4$	Upward (<0.001)	-	-	-	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

* Lag data shown as quarters (zero means that the result is significant and an effect without delay); - not estimated; SE standard error; NS non-significant


AMB
FLU
KET
ITR
POS
VOR
Use (DDD/1,000/day)
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
Posaconazole and Voriconazole listed
AMB delisted
Ketoconazole removed Dec 2013
Collection of under co-payment data April 2012 (mainly on fluconazole)
Restricted benefit listing of fluconazole and itraconazole April 2016
2005Q1
2005Q3
2006Q1
2006Q3
2007Q1
2007Q3
2008Q1
2008Q3
2009Q1
2009Q3
2010Q1
2010Q3
2011Q1
2011Q3
2012Q1
2012Q3
2013Q1
2013Q3
2014Q1
2014Q3
2015Q1
2015Q3
2016Q1
2016Q3
Year of supply (quarter)






a
Posaconazole tablets listed 1 Sept 15
Oral suspension
Total
100 mg tablet
2500
2000
1500
1000
500
0
2009Q1
2009Q3
2010Q1
2010Q3
2011Q1
2011Q3
2012Q1
2012Q3
2013Q1
2013Q3
2014Q1
2014Q3
2015Q1
2015Q3
2016Q1
2016Q3
b
Voriconazole prophylaxis listing 1 Dec 14
Oral suspension
50 mg tablet
200 mg tablet
1600
1400
1200
1000
800
600
400
200
0
2009Q1
2009Q3
2010Q1
2010Q3
2011Q1
2011Q3
2012Q1
2012Q3
2013Q1
2013Q3
2014Q1
2014Q3
2015Q1
2015Q3
2016Q1
2016Q3
c
Oral suspension
50 mg tablet
200 mg tablet
250
200
150
100
50
0
2014Q4
2015Q1
2015Q2
2015Q3
2015Q4
2016Q1
2016Q2
2016Q3
Use (prescriptions)
Year of supply (quarter)