CSIRO PUBLISHING

Australian Health Review, 2021, 45, 704–717
https://doi.org/10.1071/AH20330

Effect of a state hospital formulary on medicines utilisation in Australia

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Abstract.

Objective. The provision of medicines through state public hospitals is comparatively restrictive compared with the federally funded Pharmaceutical Benefits Scheme (PBS). Individual states are progressively moving towards statewide medicines formularies. Although a statewide formulary has existed in Queensland for some time. The effects of hospital formularies on medicines utilisation and policy in Australia has not been quantified. Thus, the aim of the present study was to quantify the effects of the Queensland Health List of Approved Medicines (LAM) on medicines utilisation in Queensland at a state and PBS-purchasing level and describe the implications for medicines policy.

Methods. This study used a quasi-experimental design with an interrupted time series (with control for PBS) examining utilisation effects of medicines within the therapeutic classes of proton pump inhibitors and non-vitamin K oral anticoagulants with LAM listing or delisting.

Results. The LAM was demonstrated to be highly effective at controlling utilisation within Queensland Health purchasing. Effects on PBS utilisation were evident, resulting in increases in generic utilisation (where available) and associated reduced total costs both within Queensland Health and to the PBS. The full benefit is likely underestimated due to limitations in the PBS datasets.

Conclusion. The LAM is a highly effective state medicines policy tool with demonstrable effects on PBS utilisation. With increased use of statewide medicines formularies, this will be an increasingly relevant aspect of Australia's overall medicines policy.

What is known about the topic? State medicines policy is comparatively restrictive compared with the federal PBS. Most Australian states have, or are developing, statewide medicines formularies.

What does this paper add? By examining several classes of medicines, a substantial quantitative effect of the Queensland state formulary on both state and PBS medicines utilisation can be demonstrated. Increased use of generic medicines and reduced costs are seen.

What are the implications for practitioners? With increased use of state medicines formularies, state medicines formularies will become increasingly relevant to medicines policy makers and advocates at both the state and federal level.

Keywords: epidemiology, health economics, health funding and financing, health policy, pharmaceuticals, medicines formularies, Pharmaceutical Benefits Scheme, policy makers.

Received 17 November 2020, accepted 11 January 2021, published online 8 November 2021

Introduction

The Pharmaceutical Benefits Scheme (PBS) is a foundational component of the Australian social health insurance system.[1,2] The national formulary, the Schedule of Pharmaceutical Benefits (https://www.pbs.gov.au/browse/publications), defines which medicines are subsidised by the federal government. The Pharmaceutical Benefits Advisory Committee (PBAC), established in 1953,[1] recommends to the Minister of Health which medicines should be listed on the formulary.

The current expenditure of the PBS is A$11 690 million per annum.[3] Like all social health insurance schemes, the value and affordability of the PBS is questioned.[4,5] Much of the debate is

levelled at price-setting mechanisms. Comparisons to other jurisdictions have demonstrated higher per capita expenditure and a higher mean price of pharmaceuticals, particularly compared with more restrictive schemes, such as New Zealand's Pharmaceutical Management Agency (PHARMAC).[6,7] There is considerably commentary on mechanisms to reduce medicine prices on the PBS.[7–11]

Comparatively less commentary is devoted to the effect of medicines utilisation on expenditure within the PBS. Analyses of statin purchasing suggest that relative utilisation, rather than price, accounts for most of the increased expenditure within the PBS.[12,13] Mechanisms on the supply and demand side exist to control utilisation in the PBS. These mechanisms include educational support through the National Prescribing Service, Therapeutic Group Premium copayments for higher-priced products and generic switching at the pharmacy level.[5,12]

The provision of public hospital services in Australia is the jurisdiction of state governments. Access to the PBS was restricted for public hospital services, but changes to legislation have allowed access for general out-patient and discharge prescriptions (in most states) and medicines listed in the Highly Specialised Drug (HSD) program.[14] Most in-patient medicine supply remains outside the PBS. In contrast with the PBS, state medicines policy is comparatively restrictive through medicines formularies (Table 1). Formularies were historically curated at individual hospital level, as remains the process in the two most populous states, New South Wales and Victoria, as well as in the Australian Capital Territory. Other states have introduced and continue to develop statewide medicines formularies. For example, the South Australian Medicines Formulary framework was first published in March 2013, but the inclusion of all therapeutic groups was not completed until 2018. The formulary is currently less restrictive than the formulary committee intends long term.[16] Similarly, development of the Western Australia Statewide Medicines Formulary (SMF) commenced in 2015 with the supporting SMF Policy enacted January 2018.[14,17] Tasmania commenced early implementation of The Tasmanian Electronic Medicines Formulary in June 2013,[18] with the formulary maturing after early implementation. The Northern Territory also has a statewide medicines formulary list.

In contrast, Queensland has a long history (Fig. 1) of state formulary management supported by the only central government procurement and warehouse facility.[14,20] The formulary, the List of Approved Medicines (LAM), is maintained by the Queensland Health Medicines Advisory Committee (QHMAC). The LAM is limited: listing one or two pharmaceuticals within a therapeutic group is typical.[20] As is common with restrictive medicines formularies, access to non-listed medicines for patients with specific clinical need is available through a prior approval process ('individual patient approval').

Despite the shift towards state hospital formularies, their effects on medicines utilisation have not been described. The

Table 1. Comparison of state pharmaceutical governance

Data from the Department of Health, Australian Healthcare Associates[14] and the Australian Bureau of Statistics[15]

State or territory	Population	Formulary	Purchasing and distribution[A]
New South Wales	8 046 100	Hospital formularies	Direct by hospital through commercial distribution channels
Victoria	6 526 400	Hospital formularies	Direct by hospital through commercial distribution channels
Queensland	5 052 800	State formulary	Through a central government procurement agency and warehouse
Western Australia	2 606 300	State formulary	Direct by hospital through commercial distribution channels
South Australia	1 742 700	State formulary	Direct by hospital through commercial distribution channels
Tasmania	531 500	State formulary	Direct by hospital through commercial distribution channels
Australian Capital Territory	423 800	Hospital formularies	Direct by hospital through commercial distribution channels
Northern Territory	245 900	State formulary	Direct by hospital through commercial distribution channels

[A]All states have some form of central tender and procurement process for all or a selection of therapeutic agents.

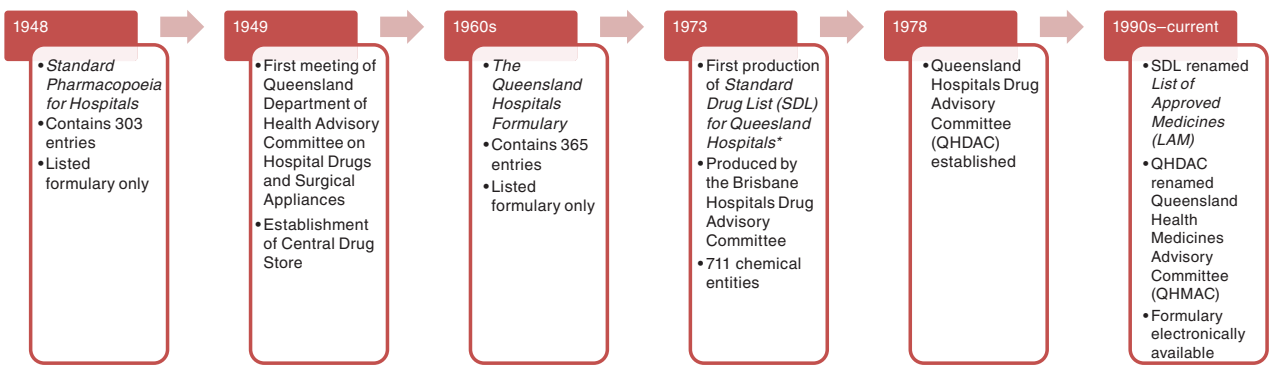

Fig. 1. History of medicines governance in Queensland Health.[19] *The SDL incorporated many of the current governance processes, such as restrictions for certain prescribers or indications, a prior authority process for non-listed agents, the requirement for evidence of clinical advantage over current agents and intent to minimise duplication within therapeutic groups.

purpose of this study was to describe and quantify the effects of the Queensland Health (QH) LAM on medicine utilisation within Queensland.

Methods

Two therapeutic groups of medicines, namely proton pump inhibitors (PPIs) and non-vitamin K oral anticoagulants (NOACs), were selected based on having several competitive agents, with at least some considered to be substitutable based on contemporary clinical guidelines. A third class, statins, was also reviewed, but opportunity for an interrupted time series (ITS) analysis was limited due to a lack of relevant LAM listing alteration within the available data periods. Substitutability was established by a review of Australian and international clinical guidelines. For PPIs the three most commonly used medicines (pantoprazole, omeprazole and esomeprazole) were selected for specific review, whereas for NOACs the two Factor Xa inhibitors (rivaroxaban and apixaban) were selected for review.

Purchasing data (available from August 2003) were extracted from the QH pharmacy information system i.Pharmacy version 8.1.0 (Computer Sciences Corporation). Dates of LAM listing were extracted from QHMAC minutes. PBS utilisation (available from January 1992) was extracted from Medicare Statistics – PBS item reports (https://www.humanservices.gov.au/corporate/statistical-information-and-data/medicare-statistics). PBS item numbers, including historical item numbers, and PBS listing dates were determined by searching PBS schedules (http://www.pbs.gov.au/info/publication/schedule/archive; available online from 2003). Utilisation was converted to defined daily dose (DDD; https://www.whocc.no/atc_ddd_index) per 1000 persons.[15] Data were considered from time of market entry (or data availability, where applicable) through to December 2018.

For PPIs, four periods of analysis were identified. For pantoprazole: Period 1, November 1995–January 2001 (off LAM); Period 2, February 2002–April 2005 (on LAM); Period 3, May 2005–May 2013 (off LAM); and Period 4, June 2013–December 2018 (on LAM). For omeprazole: Period 1, January 1992–January 2001 (on LAM); Period 2, February 2001–May 2005 (off LAM); Period 3, May 2005–June 2013 (on LAM); and Period 4, June 2013–December 2018 (off LAM).

For NOACs, specifically rivaroxaban, two periods were identified: pre- (January 2013–June 2013) and post-LAM (June 2013–December 2018) listing.

Data were analysed with Stata SE Version 15.1 (StataCorp). A quasi-experimental design using ITS analyses was used with ordinary least squares segmented regression with one autocorrelation lag and Newey–West standard errors (given evidence of heteroscedasticity in some datasets) using the *itsa* Stata module.[21] The significance of slope and level changes was evaluated using *t*-tests. PBS utilisation was tested using multiple-group methodology to construct controlled ITS. A quasi-control group was constructed including all states and territories of Australia excluding Queensland. Preintervention trends were inspected visually to ensure comparable trends between the control and intervention groups. Exclusion of one or more individual states was considered to improve the match, but not required.

Autocorrelation testing for PBS claims using Cumby–Huizinga testing was performed. Where seasonality presence was detected, AutoRegressive Integrated Moving Average (ARIMA) modelling with segmented regression of an exogenous indicator variable, LAM listing, was performed.

Given cost savings from closed formulary medicines management systems are typically realised in settings where one or more on-patent medications competes against one or more substitutable generic medications, a relevant time period where this condition was met was selected for PPIs to illustrate potential cost savings. Historical pricing for QH purchasing was extracted from i.Pharmacy. Historical PBS government purchasing costs were estimated from PBS Expenditure and Prescription reports[3] (annual government cost divided by script volume for the relevant medication). Additional patient costs were not included.

Given state hospital purchasing data outside of Queensland were not available, a robust comparator group could not be constructed. Hence, to illustrate potential total cost savings at the state hospital level, it was naïvely assumed that relative within-class PPI utilisation would match Australian (excluding Queensland) PBS utilisation and that total PPI volume would remain fixed during the relevant period. Illustrative cost savings were estimated based on these assumptions and historical price estimates.

Similar naïve assumptions were made to determine potential government PBS cost savings within Queensland, this time assuming relative within-class PPI PBS utilisation in Queensland would match Australian (excluding Queensland) PBS utilisation and that total PPI volume would again remain fixed. Given a constructed comparator group existed for this analysis, a second analysis using the estimated slope effects (mean price differences multiplied by slope, time and population) from the controlled ITS analysis was used to estimate illustrative cost savings attributable to the LAM once potential confounding factors had been considered.

Ethics approval for the study was provided by the Metro South Human Research Ethics Committee and permission to use QH data was granted by the Chief Executive Officer, Health Support Queensland.

Results

Proton pump inhibitors

PPIs are approved for use by the Australian Therapeutics Good Administration (TGA) for symptomatic relief of gastro-oesophageal reflux disease, peptic ulcer disease and Zollinger–Ellison syndrome. Australian and international guidelines do not preference PPIs, providing class recommendations.[22,23] Dates of first availability are listed in Table 2 and PBS utilisation is shown in Fig. 2.

LAM and QH purchasing

In effect, several therapeutic switches between omeprazole and pantoprazole have occurred on the LAM. QH purchasing of the three most used PPIs in Australia is shown in Fig. 3.

Interrupted time series analysis of QH purchasing confirms a highly significant effect of LAM listing on QH purchasing (Figs 4, 5). Near complete therapeutic switches (evidenced by a change in levels of between 26.5 and 46.6 DDD per 1000 persons) were seen with LAM change.

Table 2. First available dates for PPIs on the PBS and as generic medicines and LAM listing dates

Therapeutic agent	First available date on PBS	First available date generic	LAM listing dates
Omeprazole	January 1992	Prior to August 2003	January 1992–January 2001 May 2005–June 2013
Lansoprazole	August 1994	April 2010	December 1994–November 2001
Pantoprazole	November 1995	April 2010	February 2001–April 2005 June 2013–current
Rabeprazole	May 2001	December 2012	Not listed
Esomeprazole	August 2002	August 2014	Not listed

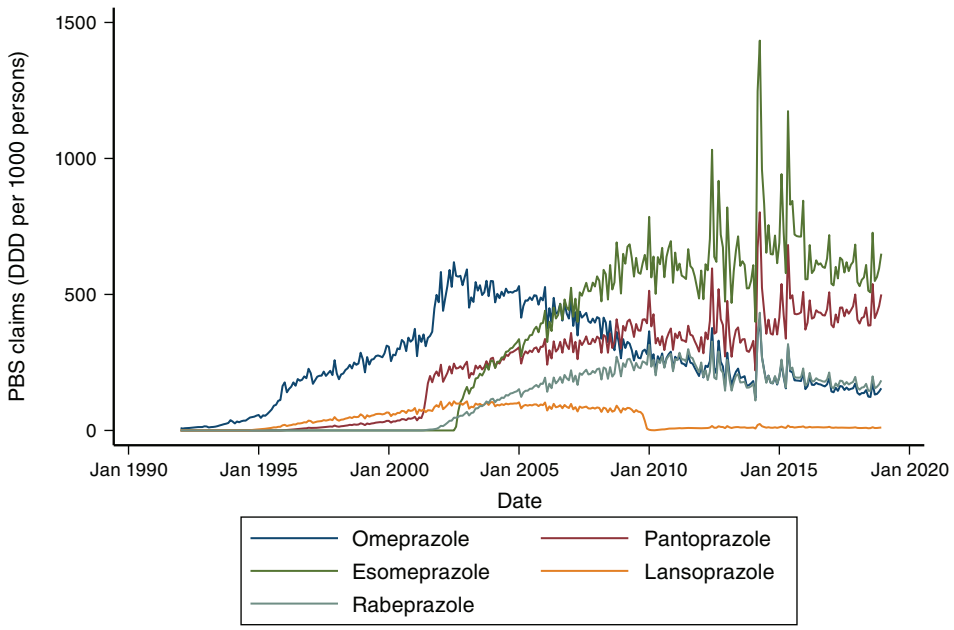

Fig. 2. PBS Claims (by month) for all PPIs.

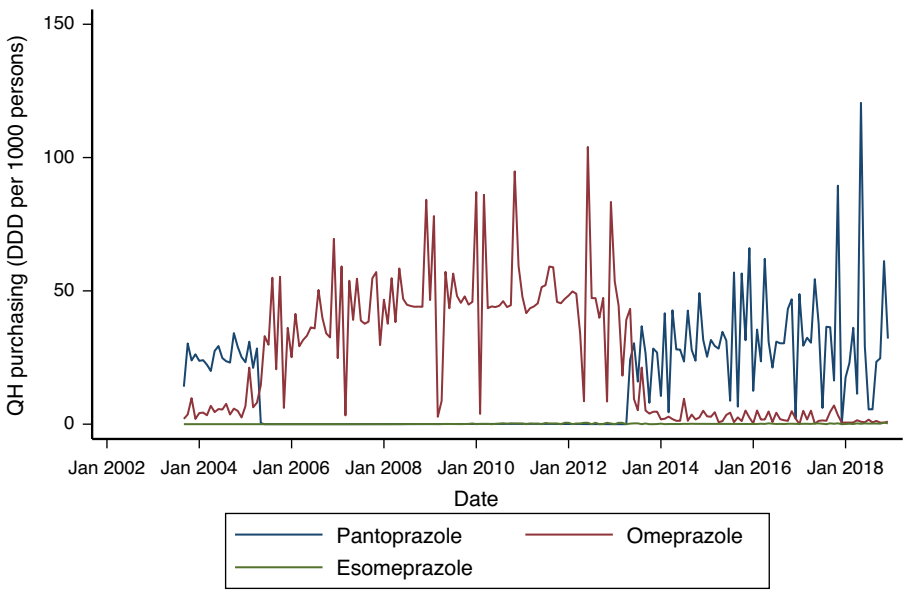

Fig. 3. Queensland Health purchasing (by month) of PPIs. Purchasing is expressed as DDD per total Queensland population.

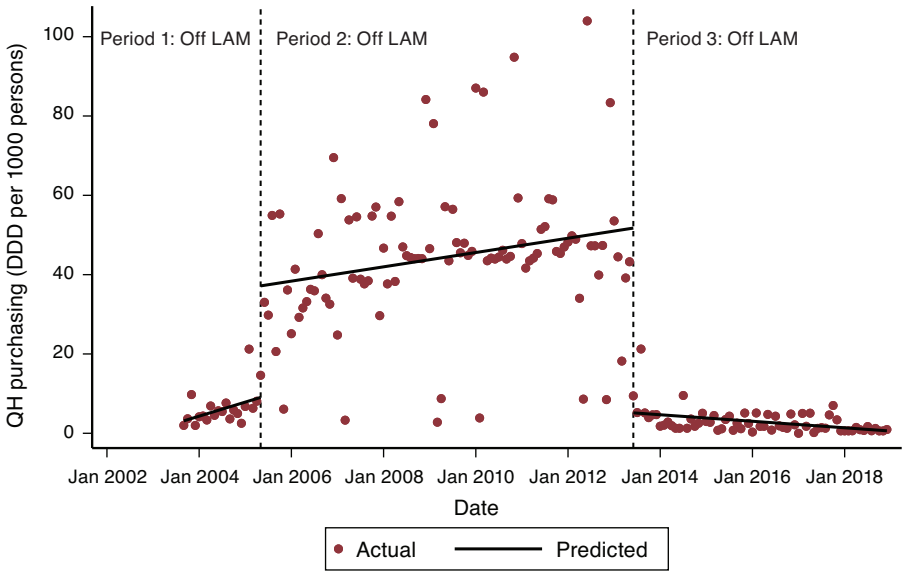

Fig. 4. Interrupted time series analysis of Queensland Health purchasing of omeprazole. Purchasing is expressed as DDD per total Queensland population. Regression with Newey–West errors and one lag.

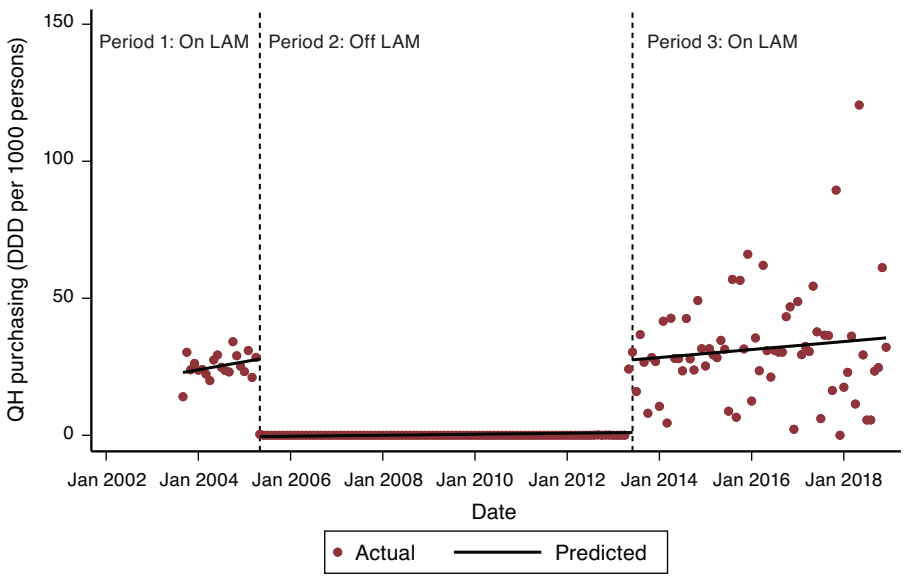

Fig. 5. Interrupted time series analysis of Queensland Health purchasing of pantoprazole. Purchasing is expressed as DDD per total Queensland population. Regression with Newey–West errors and one lag.

LAM and PBS

Interrupted time series analysis is shown in Fig. 6 and presented in Table 3. Treatment groups were comparable in the preintervention period (Period 1). Pantoprazole utilisation increased continuously across the four periods of analysis in the non-Queensland states, with a large increase in utilisation (early market uptake) at the commencement of Period 2 (97.3 DDD per 1000 persons; 95% confidence interval (CI) 54.56–140.03 DDD per 1000 persons), also seen in Queensland with no significant interaction with Queensland and the control states ($P = 0.577$). After this point, utilisation differed in Queensland, with changes in slope occurring with LAM change breakpoints (statistically significant except for Period 4). Post-trend coefficients for Queensland and non-Queensland (control) states are listed in Table 4. LAM listing between February 2001 and April 2005 was associated with an increase in pantoprazole use in Queensland of 2.01 DDD per 1000 persons per month (95% CI 0.34–3.69 DDD per 1000 persons per month), and delisting between May 2005 and February 2013 was associated with a decline of –1.99 DDD per 1000 persons per month (95% CI –2.57, –1.40 DDD per 1000 persons per month).

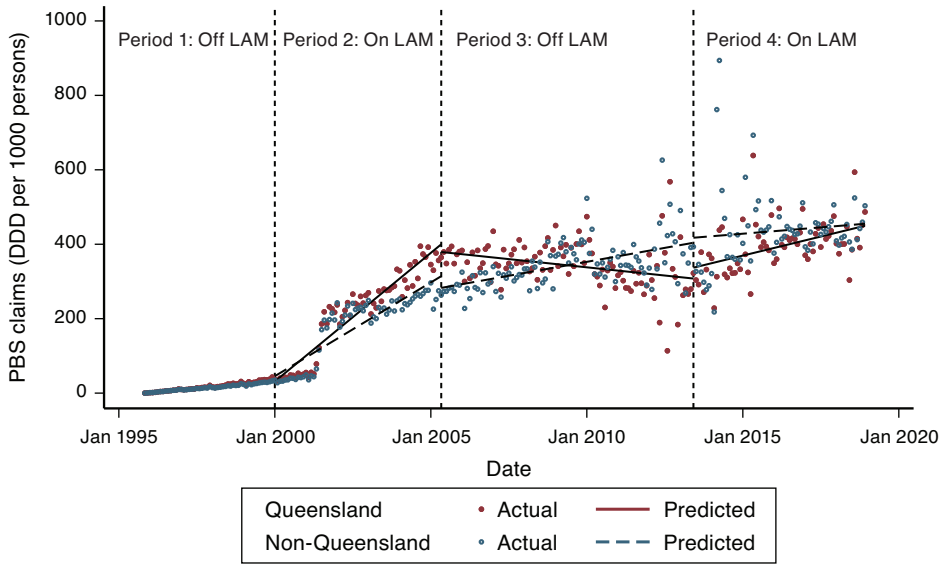

Fig. 6. Controlled interrupted time series analysis of PBS claims (by month) for oral pantoprazole. Regression with Newey–West errors and one lag.

Table 3. Controlled interrupted time series for pantoprazole with Newey–West errors and one lag

Parameter	DDD per 1000 persons per month (95% CI)		Difference	
	Queensland	Non-Queensland states and territories (control)	DDD per 1000 persons per month (95% CI)	*P*-value
Period 1: Off LAM November 1995–January 2001				
Slope		0.61 (0.57, 0.64)	0.15 relative interaction (0.08, 0.21)[A]	<0.001
Period 2: On LAM February 2001–April 2005				
Post-trend slope	5.02 (3.90, 6.14)	3.00 (1.76, 4.24)	2.01 (0.34, 3.69)	<0.001
Period 3: Off LAM May 2005–May 2013				
Post-trend slope	–0.74 (–1.13, –0.35)	1.25 (0.81, 1.69)	–1.99 (–2.57, –1.40)	<0.001
Period 4: On LAM June 2013–December 2018				
Post-trend slope	1.71 (0.95, 2.46)	0.57 (–1.17, 2.31)	1.14 (–0.76, 3.30)	0.24

[A]Note a statistical difference is seen, related to limited variance in the early market uptake period, but the magnitude is very small and graphically the groups are similar (Fig. 5).

Table 4. Controlled interrupted time series for PBS claims for oral omeprazole with Newey–West errors and one lag

Parameter	DDD per 1000 persons per month (95% CI)		Differences	
	Queensland	Non-Queensland states and territories (control)	DDD per 1000 persons per month (95% CI)	*P*-value
Period 1: On LAM January 1992–January 2001				
Slope		3.47 (3.25, 3.68)	–0.15 relative interaction (–0.46, 0.16)	0.34
Period 2: Off LAM February 2001–May 2005				
Post-trend slope	–3.30 (–4.60, –2.00)	–0.92 (–2.20, 0.37)	–2.40 (–4.21, –0.55)	0.01
Period 3: On LAM May 2005–June 2013				
Post-trend slope	–1.40 (–1.74, –1.03)	–3.44 (–3.78, –3.11)	2.06 (1.58, 2.55)	<0.001
Period 4: Off LAM June 2013–December 2018				
Post-trend slope	–2.12 (–2.57, –1.67)	–1.17 (–1.99, –3.35)	–0.95 (–1.89, –0.16)	0.046

Assessing the LAM effect on omeprazole utilisation was confounded by a decline in overall utilisation commencing in 2002, associated with esomeprazole market entry (Fig. 7). The use of non-Queensland states as a control allows the effect of the LAM to be estimated (Fig. 8). Treatment groups were comparable in the preintervention period (Period 1). Although omeprazole was LAM listed at this point, similarity with the control group likely reflects the lack of competitive agents available at the time.

Significant changes to slope were noted at each LAM change breakpoint ($P < 0.01$ for all). A significant change in level was noted at Period 2 (171 DDD per 1000 persons in the control groups; 95% CI 133–209 DDD per 1000 persons), but the interaction between Queensland and non-Queensland (control) states was not significant ($P = 0.84$). Post-trend coefficients for Queensland and non-Queensland (control) states are provided in Table 4. Delisting of omeprazole was associated with declines of

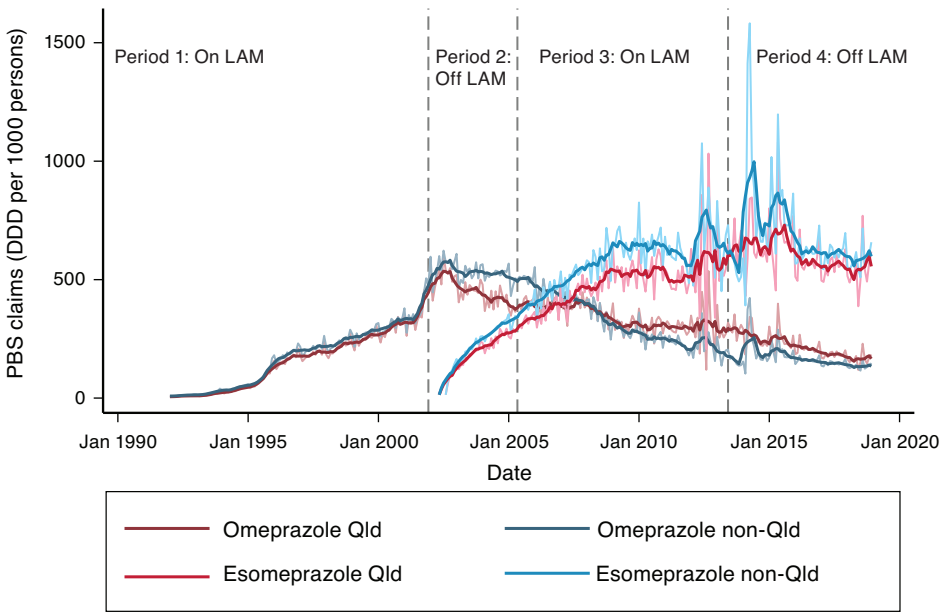

Fig. 7. PBS claims (by month) for oral omeprazole and esomeprazole. The shaded lines are actual claims data. Moving average smoothing (window 3 1 3) has been applied to the bold lines.

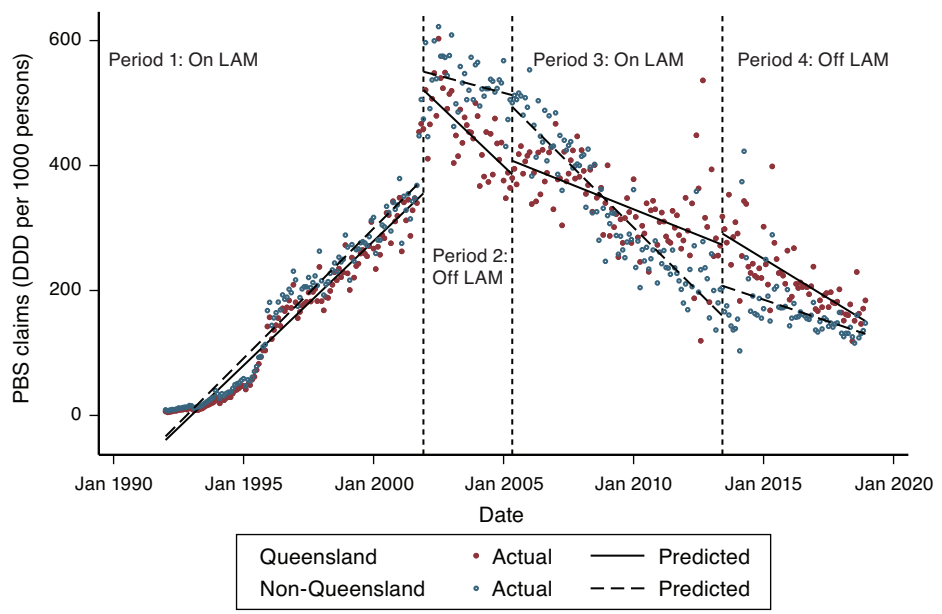

Fig. 8. Controlled interrupted time series analysis of PBS claims (by month) for oral omeprazole. Regression with Newey–West errors and one lag.

–2.40 DDD per 1000 persons per month (95% CI –4.21, –0.55 DDD per 1000 persons per month; $P = 0.01$) DDD between February 2001 and May 2005 and–0.95 DDD per 1000 persons per month (95% CI –1.89, –0.16 DDD per 1000 persons per month; $P = 0.046$) between June 2013 and December 2018, whereas listing was associated with an increase of 2.06 DDD per 1000 persons per month (95% CI 1.58–2.55 DDD per 1000 persons per month; $P < 0.001$).

Given the apparent effect of the LAM on omeprazole utilisation appears to be a reduction in the decline associated with therapeutic switching to esomeprazole, the utilisation of esomeprazole was explored. A significant reduction of 1.18 DDD per 1000 persons per month (95%CI –1.80, –0.56 DDD per 1000 persons per month; $P < 0.001$), or 18.4% less than the control states, in esomeprazole uptake on the PBS was seen in Queensland compared with non-Queensland states (Fig. 9).

Seasonality was detected on autocorrelation testing for PBS utilisation for PPIs. Segmented regression using ARIMA modelling is described and discussed in Supplementary File S1.

NOACs

NOACs, oral medications that have largely replaced the use of warfarin, are TGA listed for the prevention of stroke in atrial fibrillation and for the treatment and prevention of deep venous thrombosis and pulmonary embolism. Additional indications, venous thromboembolism prophylaxis after hip or knee replacement, exist but were not included because they are short-term, low-use indications.

Three agents are available in Australia. Dabigatran is a direct thrombin inhibitor and rivaroxaban and apixaban are direct Factor Xa inhibitors. Based on available evidence, the three are generally considered therapeutically comparable (Table 5)

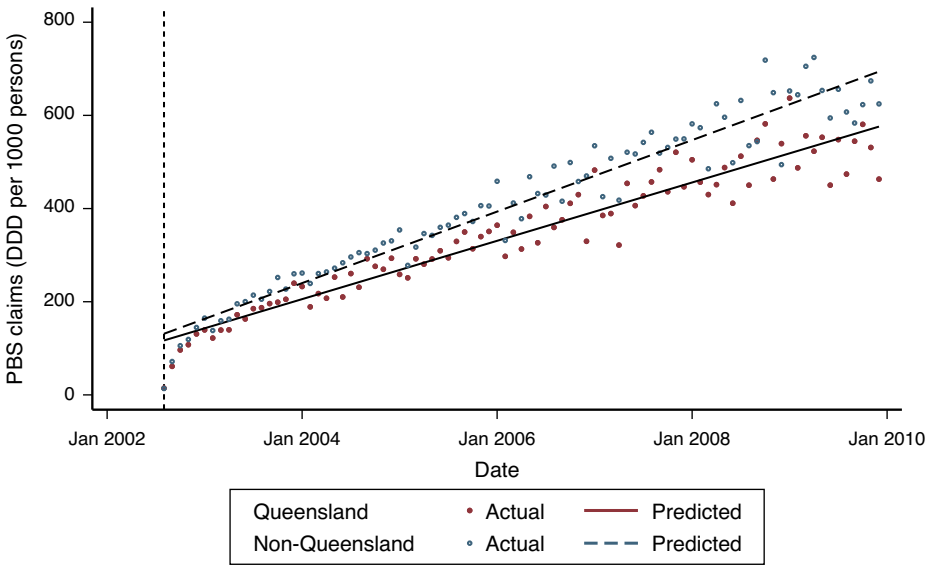

Fig. 9. Regression (Newey–West errors and one lag) of PBS claims (by month) for esomeprazole.

Table 5. Summary of guideline recommendations for NOACs

ACC, American Cardiac Consortium; AF, atrial fibrillation; AHA, American Heart Association; CHEST, The American College of Chest Physicians; CSANZ, Cardiac Society of Australia and New Zealand; DVT, deep vein thrombosis; ESC, European Society of Cardiology; HRS, Heart Rhythm Society; NHF, National Heart Foundation; PE, pulmonary embolism; THANZ, Thrombosis and Haemostats Society of Australia and New Zealand

Guideline author	Indication	Equivalence
eTG, Cardiovascular (https://tgldcdp.tg.org.au/etgcomplete)	AF, proximal DVT/PE	No recommendation of preferred agent for AF Apixaban/rivaroxaban preferred to dabigatran[A]
THANZ[24]	Treatment of DVT/PE	DOACs equivalent 'for most patients' Factor Xa inhibitors (apixaban, rivaroxaban) preferred to dabigatran for initiation of therapy in proximal DVT and PE[A]
CHEST[25]	Treatment of DVT/PE	All DOACs equivalent in recommendation
NHF of Australia/CSANZ[26]	AF	All DOACs equivalent in recommendation
AHA/ACC/HRS[27]	AF	All DOACs equivalent, Level 1:B recommendation
ESC[28]	AF	All DOACs equivalent, Level 1:A recommendation

[A]These guidelines reference the need for parenteral therapy on initiation of treatment with dabigatran as the reason for the preference for Factor Xa inhibitors.

in published guidelines. Guidelines typically highlight differences in pharmacokinetics, pharmacodynamics and dosing schedules and often indicate the importance of individual patient factors in determining appropriate therapy. Indirect comparisons and observational post-marketing studies of NOACs exist, and some suggest possible differences in efficacy (stroke and embolism incidence) and safety (bleeding incidence) within their study's cohort.[29] In the absence of controlled head-to-head studies, a clear consensus is yet to be reached in clinical guidelines. A discussion of the existing evidence is beyond the scope of the present study, other than to highlight that NOACs are best considered as imperfect substitutable medicines, with uncertainty regarding the magnitude and relevance of clinical outcome differences.

The dates of PBS and LAM availability for the included indications are listed in Table 6.

LAM and QH purchasing of NOACs

QH purchasing is shown in Fig. 10. The interrupted time series demonstrates a significant effect ($P < 0.001$) of LAM listing, but attributing causality is difficult given coexisting PBS listing. Visual inspection of the graph indicates less relative use of apixaban compared with Australian PBS utilisation (Fig. 11).

LAM and PBS utilisation of NOACs

The interrupted time series analysis is shown in Fig. 12 and presented in Table 7. Limited preintervention data are available because this was a new therapeutic agent to market. A relative increase in rivaroxaban use in Queensland compared with non-Queensland states is demonstrated and estimated at 1.04 DDD per 1000 persons per month (95% CI 0.50–1.58 DDD per 1000 persons per month). This equates to 38% of the Queensland PBS utilisation growth in the post-LAM listing period. Reciprocal lower utilisation of apixaban is evident in Queensland (Fig. 13).

Implications for generic utilisation and overall cost

A 9-year period (July 2005–June 2014) was chosen where a generically available PPI was the sole PPI listed on the LAM and a competitive on-patent substitute (esomeprazole) was available within the Australian pharmaceutical market.

Historical PPI cost estimates for the three most used PPIs are shown in Fig. 14.

Table 6. First availability of NOACs
AF, atrial fibrillation; DVT, deep vein thrombosis; PE, pulmonary embolism

Therapeutic agent	First available date on PBS[A]	First generic availability	LAM listing date
Dabigatran	September 2013	On patent	April 2018
Rivaroxaban	December 2012	On patent	August 2013 (DVT/PE) December 2013 (AF)
Apixaban	September 2013	On patent	Not listed

[A]Excluding venous thromboembolism prophylaxis for hip and knee replacement.

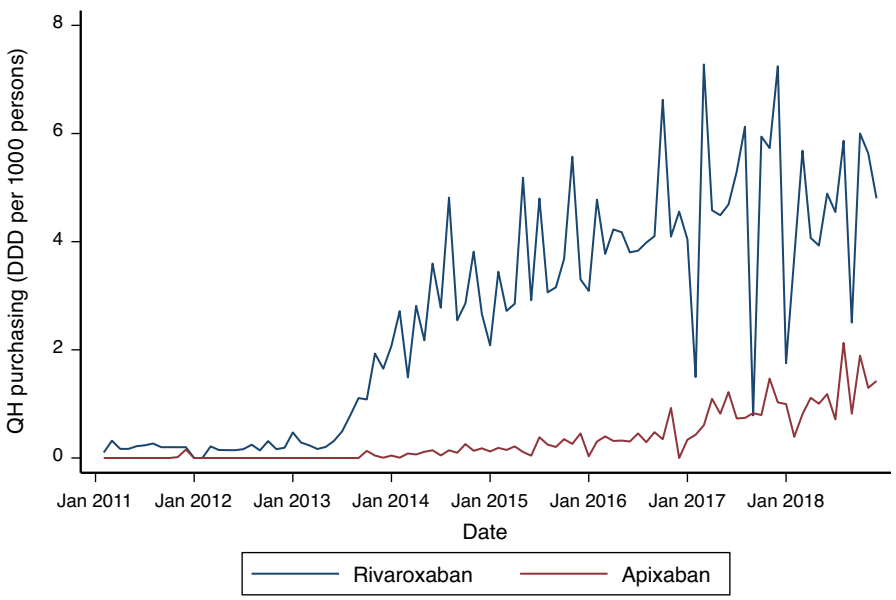

Fig. 10. Queensland Health purchasing (by month) of Factor Xa inhibitors (NOACs). Use before December 2012 reflects low utilisation after hip and knee replacement. Purchasing is expressed as DDD per total Queensland population.

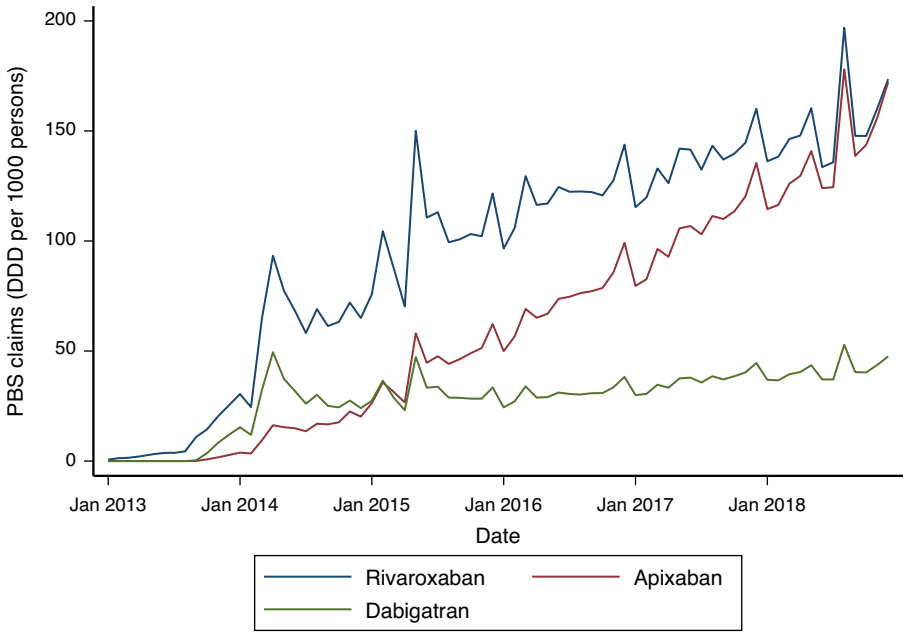

Fig. 11. Total PBS claims (by month) for all NOACs (excluding venous thromboembolism prophylaxis for hip and knee replacement).

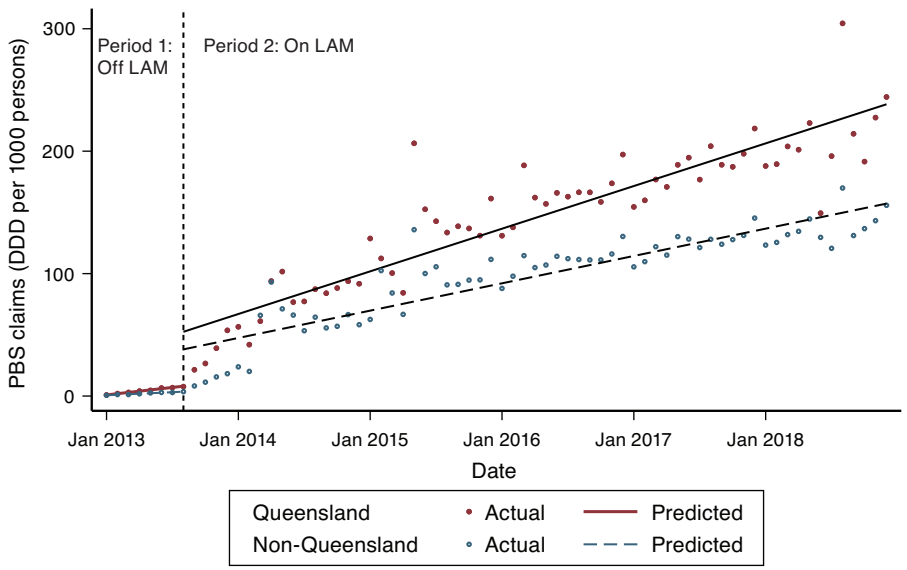

Fig. 12. Controlled interrupted time series of PBS claims (by month) for rivaroxaban before and after LAM listing. Linear regression with Newey–West errors and one lag.

Table 7. Interrupted time series analysis for PBS claims for rivaroxaban before and after LAM listing

Parameter	DDD per 1000 persons per month (95% CI)		Differences	
	Queensland	Non-Queensland states and territories (control)	DDD per 1000 persons per month (95% CI)	*P*-value
Pre-LAM listing January 2013–June 2013				
Slope	0.60 (0.52–0.68)	0.42 (0.36–0.48)	0.60 relative interaction (0.52–0.68)	<0.001[A]
Post-LAM listing June 2013–December 2018				
Post-trend slope	2.90 (2.48–3.32)	1.86 (1.5–2.2)	1.04 (0.50–1.58)	<0.001

[A]Note a statistical difference is seen, related to limited variance in the early market uptake period, but the magnitude is very small and graphically the groups are similar (Fig. 11).

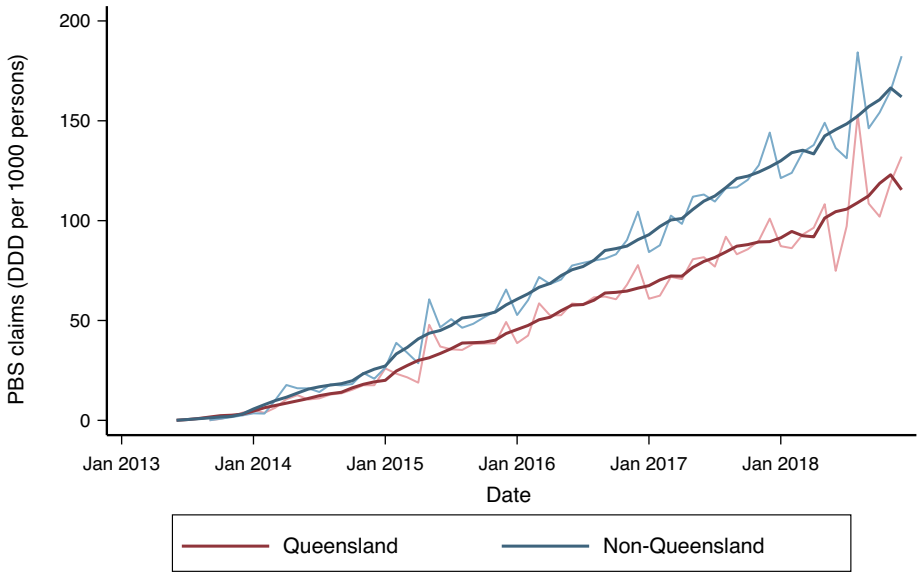

Fig. 13. PBS claims (by month) apixaban. The shaded lines are actual claims data. Moving average smoothing (window 3 1 3) has been applied to the bold lines.

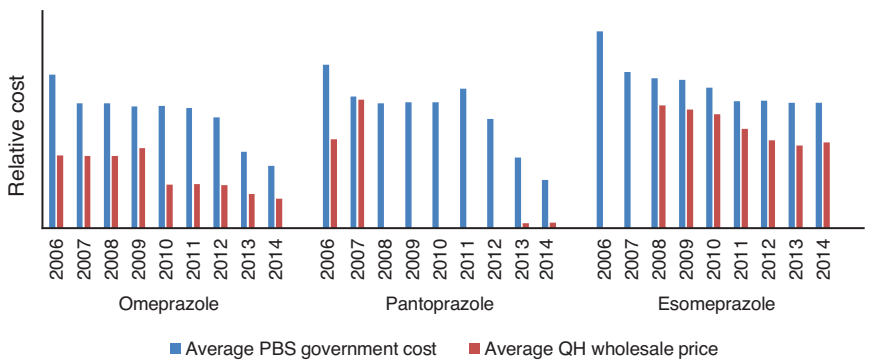

Fig. 14. Mean estimated costs for PPIs (by dispensing) by financial year (year-end). Missing values reflect lack of Queensland Health purchasing within that financial year. Actual Queensland Health prices cannot be displayed because they are commercial in confidence. PBS costs estimated as per methods from PBS data.[3]

Near complete generic use occurred within QH (99.99%). Assuming relative class utilisation would have reflected PBS utilisation, in the absence of a QH formulary, a cost saving of A$10 million over 9 years was estimated for the QH budget (based on historical QH purchase prices). Using the same methodology and applying non-Queensland PBS utilisation patterns to Queensland PBS use, there was an additional A$6.3 million in savings to the PBS over this period related to the LAM. PBS cost implications based on slope changes from the controlled ITS estimated a cost saving of A$3.5 million.

Discussion

This study describes the QH LAM and its effects on medicines utilisation within the Queensland public hospital sector, as well as secondary effects on medicines utilisation on the PBS. The LAM is demonstrated to be a highly effective policy tool for the purchasing and utilisation of medicines within Queensland hospitals. The long-standing nature of the LAM and general support among clinicians and hospital managers are likely key determinants of its effectiveness. The system has been examined for its ability to achieve lower pharmaceutical purchase prices, with evidence that QH achieves lower purchasing prices than other states and larger private pharmacy networks (Queensland Health Medicines Advisory Committee, pers. comm.). This analysis demonstrates that the ability to control utilisation is highly contributory to overall cost savings (and may be an important contributor to its success in competitive tendering). The higher use of generics and lower overall costs are consistent with known effects of formulary systems.[30–34]

This analysis further highlights the effects of the LAM that extend to wider pharmaceutical utilisation in the PBS. This is not surprising, because hospital–primary care interface effects on

medicines utilisation have been demonstrated at the patient,[35–37] prescriber[38–40] and geographic[32,41] level. Secondary effects on primary care prescribing through factors such as implicit specialist endorsement and early familiarisation have been described.[32,38,42] The present study evaluated the hospital–primary care interface at a large system level and highlights the importance of this interaction for the Australian healthcare system. These effects were clearly seen in the case of PPIs, with the serial changes in listing of PPIs on the LAM having clear effects on PBS utilisation within Queensland. These differences, of around 2 DDD per 1000 persons per month, sustained over time, result in substantial cumulative effects on PBS utilisation. For example, between February 2001 and April 2005, the estimated increase in pantoprazole use related to the LAM was 2.01 DDD per 1000 persons per month, or a difference of 100 DDD per 1000 persons in the final month of this period (equivalent to approximately one-quarter of all pantoprazole use in Queensland at the period end). Similarly, in June 2013, the retention (given overall use was declining) of omeprazole utilisation related to the LAM equated to 200 DDD per 1000 persons (or equivalent to approximately two-thirds of the total Queensland omeprazole utilisation at the period end).

The use of a quasi-experimental approach, namely controlled ITS methodology (a form of difference-in-difference testing), provides more robust estimates of effects by accounting for potential confounding effects, including time-varying effects (assuming they apply equally to the comparator groups), such as the introduction of a new competitor to market or product availability shortages.[15,43,44] The demonstration of an effect across several therapeutic classes and different time periods supports the inference of causality of the LAM on medicine utilisation in the Australian pharmaceutical market. The selection of an appropriate control in these analyses is critical.[45,46] The comparability of the non-Queensland states in preintervention periods in these analyses is reassuring. However, non-Queensland states are not a perfect control for evaluating the full effect of a hospital formulary, because hospital formulary mechanisms exist in all states (as described in the Introduction), including the maturing statewide formularies towards the later data periods, which influence PBS utilisation. Hence, the effects likely underestimate the full effects of a statewide hospital formulary such as the LAM *per se*. This study focuses solely on relative utilisation of substitutable medicines within therapeutic classes. Clearly, the total volume of medicines utilisation (and the appropriateness of the underlying prescribing) is of importance to medicines policy. Both PPIs and NOACs demonstrate increasing total utilisation over time within the Australian medicines landscape, seen in both QH and PBS utilisation data in all jurisdictions.

The availability of PBS data is a rich source for pharmacoepidemiological research,[47] but limitations exist in the PBS statistics datasets and these have been well described.[48,49] Most relevant to the present study is the absence of private and 'under copayment' (both unsubsidised) dispensing within the full statistical datasets during the available data periods. These are more prevalent with generic medicines due to their lower cost (and are therefore not relevant to the analysis of NOACs). Currently, approximately 45% of PPIs are dispensed 'under copayment'.[3] Although the 'under copayment' dispensing, by definition, does not result in direct government expenditure, its absence in the dataset results in underestimation of the true extent of generic medicine substitution. Again, this limitation is likely to further underestimate, in this case substantially, the full effects of the LAM on PPI utilisation and related cost-savings.

With the move towards statewide formularies in Australia, the potential for cost reduction exists; for example, the listing of off-patent PPIs on the LAM is associated with cost-savings of A$16.3 million on utilisation effects alone (A$10 million for QH and A$6.3 million for the PBS based on naïve assumptions) over a 9-year period. A second estimation for PBS utilisation, based on slopes from the controlled ITS, derives a cost saving of A$3.5 million. This cost saving, although smaller, better reflects illustrative cost savings causally related (i.e. once other potential confounding factors are considered) to the existence of the LAM. Regardless of the methodology, the cost savings are noteworthy, particularly in that they predominately exist through the reduced use of esomeprazole, an aggressively marketed, ever-greened medicine[35,50] with equivalent efficacy to its parent racemate omeprazole.[51] Considering these cost savings are associated with a single therapeutic group and state, potential savings extrapolated across all therapeutic groups and extended to other states may be very substantial. It should be noted that these cost savings occurred before significant reforms in PBS price disclosure arrangements for generic medicines. Potential cost savings related to increased generic medicine substitution may be greater after these reforms.

This study also demonstrates the effects of the LAM on the PBS for a fully on-patent therapeutic class, namely NOACs. A clear effect of the LAM on rivaroxaban (and reciprocal effects in apixaban) utilisation in Queensland is demonstrated. This effect is demonstrated against the background of increasing utilisation of apixaban, both within the PBS and, to a lesser degree, within QH purchasing. This growth in apixaban utilisation may relate to a perception of clinical superiority by clinicians, although second (or later) to market patent medicines are commonly associated with increasing market share, independent of whether a clinical superiority exists (esomeprazole being an example of the latter). In the case of imperfect substitutable medicines (where small but important differences in clinical outcomes between competitive products exist), additional unfavourable downstream health costs may exist and need to be considered.

Given on-patent medicines within the PBS are priced based on cost minimisation analysis, net cost savings to the health system would theoretically not be expected in this setting based on changes in relative utilisation of competing products. Competitive pricing offers to state hospital purchasers may allow cost savings at this level, although the prevalence of this is unknown. Separated pharmaceutical budgets between state and federal health systems increase the risk of counterproductive cost shifting.[35,40] If hospital systems are incentivised through competitive pricing to list more expensive on-patent medicines where generic medicines exist, a detrimental effect on the PBS budget may be seen. Periods of this occurring in QH exist: pantoprazole was solely listed on the LAM between 2001 and 2005, when generic omeprazole was available.

Applying restrictive utilisation controls to the PBS would be expected to have significant cost-saving effects. The historical, legislative and political reality[2] is that it would be extremely

unlikely that a restrictive medicines policy like QH or New Zealand's PHARMAC would be applied to Australia's PBS. Indeed, multiple contextual and implementation factors are relevant to decisions regarding national pharmaceutical purchasing models, rather than to cost alone. Utilisation control mechanisms do currently exist in the PBS, and strengthening of existing mechanisms or the introduction of others have been recommended.[5,7,12] Many current and proposed mechanisms are directed towards general practitioner prescribing, but hospital-directed approaches have received less attention. With the trend towards statewide formulary management, ensuring decision-making committees within the state public hospital system have appropriate composition, skills, experience and resourcing will be increasingly relevant to Australia's overall medicines policy and PBS costs.

Conclusion

Significant interest exists in the value and affordability of the PBS in Australia and mechanisms to improve cost-effective utilisation are frequently debated as part of Australia's medicines policy. This study provides insight into the important, but previously not well described, relationship between state hospital medicines policy and the wider PBS effects. By using a quasi-experimental methodology, a causal inference can be drawn and the significance, in terms of both volume and potential cost-implications, is substantial.

Two implications of this study should be emphasised. First, this study demonstrates the significant effects of utilisation control mechanisms on medicines cost control. Although these mechanisms may not be translatable to all settings, including the PBS itself, other demonstrated effective utilisation control mechanisms may have benefit in these settings. Second, this study highlights the significant effect that state medicines policy has on overall medicines utilisation in Australia. With increasing use of statewide medicines formularies, the importance of robust and transparent decision making that considers both a state and national perspective will continue to grow in relevance for Australian medicines policy.

Competing interests

Joel Iedema is deputy chair of the Queensland Health Medicines Advisory Committee.

Declaration of funding

This research did not receive any specific funding.

Acknowledgements

Kind thanks to Stephanie Boydell for extracting the dates of LAM listing from QHMAC minutes and to Sara Machado, London School of Economics, for providing supervisory assistance of this work for Dr Iedema's MSc dissertation.

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