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A 3-Dimensional View of Access to Licensed and Subsidized Medicines under Single-Payer Systems in the US, the UK, Australia and New Zealand

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Abstract

Introduction: Patients' access to medicines can be profoundly affected by the decisions made by medicine licensing bodies and public reimbursement agencies. The present study compares access to licensed and subsidized medicines under a single-payer system in each of the US, the UK, Australia and New Zealand (NZ). These systems are the US Department of Veterans Affairs National Formulary (VANF), the UK NHS for England and Wales, Australian Pharmaceutical Benefits Scheme (PBS) and NZ's Pharmaceutical Management Agency (PHARMAC). The VANF, PBS and PHARMAC all use positive lists of medicines that are subsidized, along with pharmacoeconomic analysis and price negotiations with suppliers. The NHS uses a negative list of medicines that are *not* to be subsidized, along with pharmacoeconomic analysis of a small number of medicines and caps on manufacturers' profits.

Objective: Our objective was to compare licensed and subsidized medicines in terms of the following: (i) total numbers of entities (unique Anatomical Therapeutic Chemical [ATC] codes); (ii) times since first registration (age) of the entities; and (iii) numbers of innovative entities.

Methods: This was an observational study in order to test pre-defined hypotheses. All products listed in a major prescribing reference in each country were included in the study. All products were classified by ATC code and their registration dates recorded. Products were collapsed by ATC code to determine 'best-case' licensing and subsidy for each entity, along with the date of first registration. Innovative entities selected for 'fast-track' approval by the US FDA or as a 'breakthrough or substantial improvement' by the Canadian Patented Medicines Prices Review Board were identified. Results were verified by a sensitivity analysis that excluded entities only available in injectable formulations (as these may not always be listed in general

prescribing references), and by a parallel analysis done by active agent rather than ATC code.

Results: Of the 918 entities and 64 innovative entities licensed in the US, 505 and 20, respectively, were subsidized by the VANF. In the UK, this was 1020 and 58 (1016 and 58 NHS subsidized); in Australia, this was 879 and 49 (567 and 30 PBS subsidized); and in NZ, this was 765 and 39 (503 and 19 PHARMAC subsidized). With the exception of the UK, entities licensed in the US were newer than elsewhere. The median ages were as follows: 6607 days in the US (VANF subsidized 8203 days; $p < 0.001$); 7319 days in the UK (NHS subsidized 7319 days; $p = 0.903$); 7795 days in Australia (PBS subsidized 8065 days; $p = 0.406$); and 8936 days in NZ (PHARMAC subsidized 10 724 days; $p < 0.001$). NHS subsidized entities were newer than elsewhere. VANF and PHARMAC subsidized entities were significantly older than licensed entities in their respective countries.

Conclusion: The single-payer systems examined differ in the number and age of licensed and subsidized entities, along with access to innovative entities. The NHS subsidized the most entities, the newest entities and the most innovative entities. NZ's PHARMAC system subsidized the fewest and oldest entities, and the fewest innovative entities. The VANF and PBS consistently fell between the other two systems in terms of the number of subsidized entities, age of subsidized entities and number of subsidized innovative entities.

Key points for decision makers

- The present study compares access to medicines under nationwide single-payer systems in four countries (the US, the UK, Australia and New Zealand) in terms of the number of entities, the age of the entities and the number of innovative entities that are licensed and subsidized
- The UK's NHS subsidized the most entities, the newest entities and the most innovative entities
- New Zealand's Pharmaceutical Management Agency (PHARMAC) subsidized the fewest entities, the oldest entities and the fewest innovative entities
- These differences may be related to the different cost-containment measures and budgetary constraints in these systems

Introduction

Patients' access to medicines can be profoundly influenced by the decisions made by public reimbursement agencies, which subsidize the cost of medicines for individual patients. Access can also be influenced by medicine licensing agencies, which give approval for medicines to be marketed in a country. The present study compares the number, age and innovation of medicines licensed in the US, the UK, Australia and New Zealand (NZ), and of medicines subsidized under a publicly funded single-payer system in each of these countries. These systems are the US Department of Veterans Affairs (VA) National Formulary (VANF), the UK NHS for England and Wales, the Australian Pharmaceutical Benefits Scheme (PBS), and the NZ Pharmaceutical Management Agency (PHARMAC).

There are many ways of financing and delivering healthcare in the US. The majority of US

residents have private health insurance, and there are large public programmes such as Medicare (which covers almost all people 65 years of age and above), Medicaid (which covers many but not all people with low incomes and few assets) and military medicine (which includes Tricare for active service members and their families, as well as the VA).[1] The VA health system is not intended to be representative of this large and diverse health system. Rather, the VA health system was chosen for this study because it is a large US health system that shares many similarities with the health systems of the UK, Australia and NZ, and thus provides a starting point for international comparison. Researchers have also in the past looked to the VA for lessons on formulary management and comparative effectiveness that can be applied elsewhere in the US health system.[2,3]

Eligible VA patients (see table I) can access primary and secondary care at VA health facilities across the US. The VANF is a positive formulary of medicines that must be available at all VA facilities. The VA uses cost-minimization and cost-effectiveness analyses implicitly as part of its formulary guidelines when evaluating changes to the VANF, and negotiates pharmaceutical prices with manufacturers. (Evaluation and price negotiation are done by different bodies within the VA.) Cost-control measures include competitive bid-

Table I. Key features of each single-payer system ($US, year 2007 values)

Features	VANF	UK NHS	PBS	PHARMAC
Covers all residents of nation	No[a]	Yes	Yes	Yes
Type of formulary	Positive list	Negative list	Positive list	Positive list
Pharmacoeconomic analysis	CMA, CEA[b]	CUA[c]	CMA, CEA, CUA	CUA
Decisions on which treatments to fund	At national level	At local level[d]	At national level	At national level
Price negotiations with suppliers	Yes	No[e]	Yes	Yes
Capped national pharmaceutical budget	No	No	No	Yes
2007 prescription co-payments[f]	$US8	$US0 or $US13.7[g]	$US4.1 or $US25.7[h]	$US0 to $US11 (most paid $US2.2)
2007 yearly co-payment limits	$US960 (most patient groups)	None[i]	$US229.6 or $US886.1[h]	20 co-payments per family

a Covers veterans of the US armed forces, and in some cases their dependents, members of the Reserves and National Guard, and veterans of countries allied with the US in some conflicts. Enrolment is limited, and priority is given to veterans with service-related disabilities and limited incomes.

b Used as part of formulary management guidelines.

c NICE only evaluates selected treatments, typically those that are controversial, high cost or have the potential for a major impact on the NHS budget.

d All treatments that have had a positive evaluation from NICE have to be funded across the country.

e Suppliers set their own prices at market launch of the drug, in exchange for caps on maximum profit and across-the-board price cuts on all their products at agreed times.

f VANF co-payments are per each 30-day supply of medicines; all others are per prescription. All four systems use income-based co-payments or co-payment exemptions (or both) to limit the cost to patients.

g English patients paid $US13.7 per prescription, but up to 85% of prescriptions are exempt. Wales abolished prescription co-payments on 1 April 2007.

h Patients with limited incomes paid $US4.1 (safety net of $US229.6, after which co-payments were waived) and all other patients paid $US25.7 (safety net of $US886.1, after which patients paid $US4.1).

i Patients can purchase 3-month or 12-month 'prescription pre-payment certificates', which cover all co-payments in that period for a fixed price, but the onus is on the patient to do this.

CEA = cost-effectiveness analysis; **CMA** = cost-minimization analysis; **CUA** = cost-utility analysis; **NICE** = National Institute for Health and Clinical Excellence; **PBS** = Pharmaceutical Benefits Scheme; **PHARMAC** = Pharmaceutical Management Agency; **VANF** = Department of Veterans Affairs National Formulary.

ding, prescribing guidelines, the use of generics, the use of Federal Supply Schedule prices (which by law are limited to 76% of non-federal prices) and patient co-payments (see table I).[2,4-9]

All residents of England and Wales are entitled to treatment under the NHS. Pharmaceutical manufacturers enter a multi-year contract to supply the NHS under the Pharmaceutical Price Regulation Scheme (PPRS). The PPRS allows manufacturers to set their own prices in return for across-the-board price cuts at certain times and caps on maximum profit.[10,11] The NHS uses a negative list of medicines that are *not* to be subsidized. The negative list is very small, and unlike positive list systems, medicines do not have to be appraised before being eligible for funding. In theory, any marketed medicine that is not on the negative list is eligible for NHS funding. In practice, funding is controlled by regional Primary Care Trusts (PCTs), which decide health service priorities in the region.[12] This leads to some pharmaceutical treatments being subsidized in one region but not in another ('postcode prescribing'). The National Institute for Health and Clinical Excellence (NICE) evaluates a small number of medicine indications each year for clinical and cost effectiveness. PCTs are required to subsidize all medicine indications that have a positive NICE evaluation.[12,13] Year 2007 patient co-payments are in table I.[14-17]

All Australian residents are eligible for subsidized pharmaceuticals under the PBS. The PBS uses a positive formulary, is funded from federal government revenue, and subsidizes approximately 75% of all prescription costs in Australia. Manufacturers seeking a new listing on the PBS make an application to the Pharmaceutical Benefits Advisory Committee (PBAC), which considers evidence from clinical trials, drug utilization data and economic evaluation before making a recommendation. A separate body, the Pharmaceutical Benefit Pricing Authority (PBPA), negotiates the price with the manufacturer. The final listing decision is made by the Minister for Health and Ageing, or the entire Cabinet for more expensive listings.[12,15,18-24] Year 2007 patient co-payments are in table I.[15,23]

All NZ residents are eligible for subsidized medicines. These are listed in a positive formulary called the Pharmaceutical Schedule. PHARMAC manages the Schedule, evaluates medicines, makes listing decisions, negotiates with suppliers and manages a capped yearly pharmaceutical budget. Listing decisions involve advice from the Pharmacology and Therapeutics Advisory Committee (a committee of medical experts from different specialties), cost-utility analyses and total budgetary impact analyses. Cost-containment measures include the use of generics, competitive bidding (including for the right to be the sole supplier of a medicine), risk-sharing agreements, 'bundling' agreements (where a supplier offers a lower price on one drug to get another listed) and reference pricing. PHARMAC uses reference pricing at both the molecular level, and for different molecules within drug classes. Year 2007 patient co-payments are in table I.[12,15,25-30]

The cost-containment policies of each system have been described in detail elsewhere.[8,9,12,28,31,32] The key features of each system are summarized in table I.

Objective

Our objective was to compare licensed and subsidized medicines in the four countries/systems in terms of the following: (i) total numbers of entities (unique WHO Anatomical Therapeutic Chemical [ATC] codes); (ii) times since first registration ('age') of the entities; and (iii) numbers of innovative entities.

Methods

Choice of Study Countries

We considered a number of factors in selecting the countries for the present study. We limited the initial pool of countries to those that were members of the Organisation for Economic Co-operation and Development (OECD).[33] In addition, none of the countries in the study could share a way of licensing medicines, to ensure the licensing data were independent. This meant limiting the study to only one country that came under the authority of the European Medicines Agency (EMA), due to the EMA's centralized licensing procedures.[34]

Furthermore, each country in the study had to have at least one single-payer system that used a single nationwide formulary, and which had one central body that made decisions on high-cost drugs. (Systems that only used local formularies, offered multiple drug plans or which had several decision-making agencies would have made the analysis too complex.) With these factors in mind, the US, the UK, Australia and NZ were selected for the study.

Data

Collection

We collected information on licensed medicines from commonly used prescribing references in each country using previously published methods.[35] We had previously developed this methodology for carrying out large-scale comparisons of licensed and subsidized medicines between countries, and verified the methodology by publishing a comparison of NZ and Finland.[35]

Information was collected on all products listed in 2007 editions of the Physicians' Desk Reference (US),[36] electronic Medicines Compendium (UK),[37] Australian Prescription Products Guide[38] and MIMS New Ethicals (NZ).[39] A product was defined as a unique strength and formulation produced by a manufacturer. The brand name, generic name, formulation, legal status and licensing status in adults were recorded for each product.

We collected subsidy information from the online VANF (US),[40] electronic NHS Drug Tariff for England and Wales[41] and NICE website (UK),[42] online Schedule of Pharmaceutical Benefits (Australia)[43] and online Pharmaceutical Schedule (NZ) in mid-2007.[25,44] A product was considered subsidized in the VANF, Schedule of Pharmaceutical Benefits and Pharmaceutical Schedule if it was listed as being subsidized in that formulary. A product was considered subsidized by the NHS if it was listed in the electronic Medicines Compendium (i.e. was on the UK market in 2007), but was not on the negative list in the Drug Tariff and had not received a negative evaluation from NICE for all licensed indications.

Products that were only available in non-prescription forms were not included in the dataset. Medical and surgical supplies such as non-medicated dressings, barrier or mechanical contraceptives, and diagnostic strips were not included. The final dataset had 9497 products (2891 US, 3130 UK, 2109 Australia and 1367 NZ).

Handling

We sought registration dates for each product from the regulatory authorities in each of the four countries. Registration dates in the US, Australia and NZ were obtained from publicly available databases.[45-47] As the UK did not have a publicly available database of registration dates, a Freedom of Information Act request was made to the Medicines and Healthcare products Regulatory Agency. At least one registration date was found for 9390 of the 9497 products (98.87%). The earliest registration date in any of the four countries was taken as the date of first registration for that product. The time since first registration (a measure of the age of the product) was calculated by subtracting the date of first registration from 31 December 2007.

All products were classified using the ATC system.[48] ATC codes from the 2007 index were used wherever possible, but 2008 codes were used where products were not in the 2007 index.

Checking and Validation

A random sample of the licensing and subsidy information entered by one investigator was checked by another. ATC coding was undertaken by two investigators working together and checking each other's work. Three percent of registration dates were checked by a research assistant. (The research protocol called for a larger sample to be checked if the first check showed substantial errors. However, the 3% sample showed over 98% of the registration dates were accurate to the day of licensing.)

All analyses performed by ATC code were replicated by analysis by active agent to cross-check the results. A sensitivity analysis that removed entities only available in injectable form (as these would mostly be used in secondary care, and may not be listed in general prescribing

references) was performed to check for major listing differences.

Analysis

All analysis was undertaken using STATA (Version 10.0),[49] a data management and statistical analysis program for large datasets. Products were collapsed by ATC code to determine the 'best-case' licensing and subsidy for each ATC code in each country. Registration dates were collapsed by ATC code to determine the earliest date of registration for each ATC code.

We then calculated the number of entities (unique ATC level 5 codes) that were licensed and subsidized, and the earliest registration date for each licensed and subsidized entity.

In addition to the total number of unique ATC level 5 codes licensed and subsidized, the number of ATC level 4 groups that contained licensed and subsidized ATC level 5 codes were compared. This analysis was designed to compare the availability of genuine therapeutic alternatives in each country and each system by preventing large numbers of therapeutically similar agents within the same ATC level 4 group (so called 'me-too' drugs) from affecting the results.

The number of licensed and subsidized entities within categories of drugs to treat five diseases with high mortality and morbidity in all four countries (diabetes mellitus, cardiovascular disease, cancer, mental illness and respiratory disease) were also compared. This analysis was designed to identify if any country was lacking agents to treat these conditions.

The number of innovative entities was also determined using the methodology developed by Roughead et al.[50] Roughead et al. defined innovative entities as those that had been granted 'fast-track' approval by the US FDA (because these entities treated a serious or life-threatening illness and filled an unmet need), and those that had been classified as a 'breakthrough or substantial improvement' (the first drug product to effectively treat a particular illness or to provide a substantial improvement over existing drug products) by the Canadian Patented Medicines Prices Review Board (PMPRB).[50]

We therefore compiled of a list of all medicines that had been granted fast-track approval by the FDA between 1998 and 2007, and all medicines classified by the PMPRB as a 'breakthrough or substantial improvement' between 2000 and 2007.[51,52] Two vaccines were excluded from the list, as vaccination schedules and pathogen prevalence differ between countries. All 65 other entities on the list were checked to see if they were licensed or subsidized in each of the four countries in 2007.

Definitions

The following definitions are used throughout the Results and Discussion sections:

- Entity: a medicine with a unique ATC level 5 code.
- Age of entities: the time since the entity was first registered in any of the four countries in the study.
- Older: greater time since first registration.
- Newer: shorter time since first registration.
- Innovative entities: entities that meet the criteria developed by Roughead et al.[50]

Results

Number of Entities

Table II shows the number of entities licensed in each country and subsidized by each system. The UK had the most licensed entities, followed

Table II. Number of entities licensed and subsidized for adults

Country	Licensed for adults	Subsidized for adults	p-Value (chi-squared test)
US	918	505 (55.1%) VANF	0.061
UK	1020	1016 (99.6%) NHS	0.733
Australia	879	567 (64.5%) PBS	<0.001
NZ	765	503 (65.8%) PHARMAC	<0.001

NZ = New Zealand; **PBS** = Pharmaceutical Benefits Scheme; **PHARMAC** = Pharmaceutical Management Agency; **VANF** = Department of Veterans Affairs National Formulary.

Table III. Number of Anatomical Therapeutic Chemical level 4 groups that contain licensed and subsidized entities in each country

Country	Number of ATC level 4 groups that contain entities licensed for adults	Number of ATC level 4 groups that contain entities subsidized for adults	% of ATC level 4 groups that contain subsidized entities to ATC level 4 groups that contain licensed entities
US	420	296 (VANF)	70.48
UK	443	443 (NHS)	100
Australia	392	293 (PBS)	74.70
NZ	386	285 (PHARMAC)	73.80

ATC = Anatomical Therapeutic Chemical; **NZ** = New Zealand; **PBS** = Pharmaceutical Benefits Scheme; **PHARMAC** = Pharmaceutical Management Agency; **VANF** = Department of Veterans Affairs National Formulary.

by the US, Australia and NZ. The NHS had the most subsidized entities, followed by the PBS, VANF and PHARMAC. There was a statistically significant difference between the number of entities subsidized by the PBS and PHARMAC and the number licensed in their respective countries (chi-squared test $p < 0.001$), but this was not the case for the NHS or the VANF.

Table III shows the number of ATC level 4 groups that contain entities licensed in each country and subsidized in each system. Even when the effect of multiple ATC level 5 entities within a level 4 group are removed, the UK had the most groups that contained licensed entities, followed by the US, Australia and NZ. The NHS had the most groups that contained subsidized entities, followed by the VANF, PBS and PHARMAC. However, the differences between the number of groups that contained subsidized entities were much smaller than the differences in the total number of subsidized entities.

Table IV shows the number of entities licensed in each country and subsidized by each system for five conditions common in all four countries (diabetes, cardiovascular disease, cancer, mental illness and respiratory disease).

Table IV shows that all four countries have licensed options for treating these common con-

Table IV. Numbers of licensed (and subsidized) entities used in treating diabetes mellitus, cardiovascular disease, cancer, respiratory disease and mental illness

ATC group	US (VANF)	UK (NHS)	Australia (PBS)	NZ (PHARMAC)
A08. Anti-obesity preparations	4 (0)	3 (3)	4 (1)	3 (0)
A10. Drugs used in diabetes	26 (6)	30 (30)	21 (18)	16 (14)
C01. Cardiac therapy	17 (9)	20 (20)	20 (9)	19 (10)
C02. Antihypertensives	10 (6)	11 (11)	7 (6)	7 (5)
C03. Diuretics	15 (9)	15 (15)	11 (9)	10 (10)
C04. Peripheral vasodilators	2 (1)	4 (4)	3 (1)	3 (3)
C07. Beta-blocking agents	15 (8)	18 (18)	10 (9)	12 (11)
C08. Calcium channel blockers	9 (5)	11 (11)	8 (7)	7 (6)
C09. Agents acting on the renin- angiotensin system	22 (7)	24 (24)	18 (7)	12 (12)
C10. Lipid-modifying agents	15 (5)	14 (14)	10 (10)	9 (9)
L01. Antineoplastic agents	53 (30)	58 (57)	58 (38)	49 (41)
L03. Immunostimulants	16 (12)	14 (11)	13 (12)	11 (7)
L04. Immunosuppresants	19 (10)	15 (14)	17 (13)	15 (9)
N05. Psycholeptics	34 (24)	45 (43)	37 (26)	34 (31)
N06. Psychoanaleptics	32 (16)	29 (29)	29 (25)	27 (18)
R03. Drugs for obstructive airways diseases	24 (14)	23 (22)	21 (16)	17 (15)

ATC = Anatomical Therapeutic Chemical; **NZ** = New Zealand; **PBS** = Pharmaceutical Benefits Scheme; **PHARMAC** = Pharmaceutical Management Agency; **VANF** = Department of Veterans Affairs National Formulary.

Table V. Differences in median times since first registration of licensed and subsidized entities

Country	Median time since first registration – group 1 (days)	Country	Median time since first registration – group 2 (days)	Difference in medians (days)	p-Value (Wilcoxon rank-sum test)
Lic. US	6607	Lic. UK	7319	–712	0.086
Lic. US	6607	Lic. Aus	7795	–1188	<0.001
Lic. US	6607	Lic. NZ	8936	–2329	<0.001
Lic. UK	7319	Lic. Aus	7795	–476	0.017
Lic. UK	7319	Lic. NZ	8936	–1617	<0.001
Lic. Aus	7795	Lic. NZ	8936	–1141	0.007
Sub. VANF	8203	Sub. UK NHS	7319	884	<0.001
Sub. VANF	8203	Sub. PBS	8065	138	0.596
Sub. VANF	8203	Sub. PHARMAC	10724	–2521	<0.001
Sub. NHS	7319	Sub. PBS	8065	–746	0.002
Sub. NHS	7319	Sub. PHARMAC	10724	–3405	<0.001
Sub. PBS	8065	Sub. PHARMAC	10724	–2659	<0.001

Aus = Australia; **Lic.** = licensed; **NZ** = New Zealand; **PBS** = Pharmaceutical Benefits Scheme; **PHARMAC** = Pharmaceutical Management Agency; **Sub.** = subsidized; **VANF** = Department of Veterans Affairs National Formulary.

ditions. All four systems also have subsidized options for treating these conditions, with the exception of subsidized anti-obesity agents on the VANF and the PHARMAC-managed Pharmaceutical Schedule.

Age of Entities

Table V compares the differences in the age of entities licensed in the four countries and subsidized in the four systems. Entities licensed in Australia were on average older than those in the US and UK, and those licensed in NZ were on average older than those in Australia, the US and the UK. There was no statistically significant difference in the age of entities licensed in the US and the UK.

Entities subsidized by the VANF, PBS and PHARMAC were on average older than those subsidized by the NHS. Entities subsidized by PHARMAC were on average older than those subsidized by the VANF and PBS, but there was no statistically significant difference in age between entities subsidized by the VANF and PBS. Entities subsidized by the VANF and PHARMAC were on average older than those licensed in their respective countries (Wilcoxon rank-sum test $p < 0.001$), but there was no statistically significant difference in age between entities subsidized by the NHS and PBS and those licensed in their respective countries.

The numbers and ages of entities did not alter significantly when injectable-only entities were removed as a sensitivity analysis or in the parallel analysis by active agent.

Number of Innovative Entities

Table VI shows the licensing and subsidy status of each of the innovative entities in 2007, along with changes to these between the end of 2007 and April 2010.

Sixty-four of the 65 innovative entities were licensed in the US in 2007 (of which 20 were subsidized by the VANF), 58 were licensed in the UK (all subsidized by the NHS), 49 were licensed in Australia (of which 30 were subsidized by the PBS, and a further four by the Life Saving Drugs Program in 2007) and 39 were licensed in NZ (of which PHARMAC subsidized 19 entities).

Three of the entities were newly licensed in the UK between the end of 2007 and April 2010, eight were newly licensed in Australia, and eleven were newly licensed in NZ. Four were newly subsidized by the VANF in that period; ten were newly subsidized by the PBS (and a further four

Table VI. Status of innovative entities by country in 2007

	US lic. 2007	VANF sub. 2007	UK lic. 2007	UK NHS sub. 2007[a]	Aus lic. 2007	PBS sub. 2007	NZ lic. 2007	PHARMAC sub. 2007
Abacavir	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Abatacept	Yes		Yes	Yes	Yes	#	†	
Agalsidase alfa			Yes	Yes	Yes	[b]	‡	
Agalsidase beta	Yes		Yes	Yes	Yes	[b]	Yes	
Alemtuzumab	Yes		Yes	Yes	Yes		‡	
Alglucosidase alfa	Yes		Yes	Yes	†	[b]	‡	
Amprenavir	Yes		Yes	Yes	Yes		Yes	
Anastrozole	Yes	Yes[c]	Yes	Yes	Yes	Yes	Yes	Yes
Apomorphine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Arsenic trioxide	Yes		Yes	Yes	‡	##		Yes
Azacitidine	Yes	Yes	†		‡			
Bevacizumab	Yes	##	Yes	Yes	Yes	##	Yes	
Bortezomib	Yes	##	Yes	Yes	Yes	Yes	Yes	
Caspofungin	Yes		Yes	Yes	Yes		Yes	
Cetuximab	Yes		Yes	Yes	Yes	Yes	Yes	
Cinacalcet	Yes		Yes	Yes	Yes	#	Yes	
Clofarabine	Yes		Yes	Yes	‡			
Darunavir	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
Dasatinib	Yes		Yes	Yes	Yes	Yes	‡	##
Decitabine	Yes		~					
Deferasirox	Yes		Yes	Yes	Yes	Yes	Yes	
Docetaxel	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Drotrecogin alfa (activated)	Yes		Yes	Yes	Yes	Yes	Yes	
Efavirenz	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Emtricitabine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Emtricitabine, tenofovir disoproxil and efavirenz	Yes	Yes	Yes	Yes	‡	###	‡	
Enfuvirtide	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Erlotinib	Yes		Yes	Yes	Yes	#	Yes	
Etanercept	Yes		Yes	Yes	Yes	Yes	Yes	Yes
Fluocinolone acetonide[d]	Yes	[e]	~		~		[e]	
Fosamprenavir	Yes	Yes	Yes	Yes	Yes	Yes		
Galsulfase	Yes		Yes	Yes	Yes	[b]		
Gefitinib	Yes		‡		Yes	Yes	Yes	
Hydroxocobalamin[f]	Yes		Yes	Yes	Yes	Yes	Yes	Yes
Ibritumomab tiuxetan (90Y)	Yes		Yes	Yes			‡	
Ibuprofen[g]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Idursulfase	Yes		Yes	Yes	†	[b]	†	
Imatinib	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Continued next page

Table VI. Contd

	US lic. 2007	VANF sub. 2007	UK lic. 2007	UK NHS sub. 2007[a]	Aus lic. 2007	PBS sub. 2007	NZ lic. 2007	PHARMAC sub. 2007
Imiglucerase	Yes		Yes	Yes	Yes	[b]	Yes	Yes
Infliximab	Yes		Yes	Yes	Yes	Yes	Yes	
Interferon gamma	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
Lapatinib	Yes		†		Yes	#	Yes	
Laronidase	Yes		Yes	Yes	Yes	[b]	Yes	
Lenalidomide	Yes	##	Yes	Yes	Yes	##	†	
Levofloxacin	Yes	Yes	Yes	Yes				
Lopinavir and ritonavir	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Miglustat	Yes		Yes	Yes	Yes	[b]	‡	
Nelarabine	Yes		Yes	Yes				
Nitisinone	Yes		Yes	Yes	~			
Oxaliplatin	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Paclitaxel	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Palifermin	Yes		Yes	Yes	Yes			
Panitumumab	Yes		Yes	Yes	†			
Pegaptanib	Yes		Yes	Yes			Yes	
Peginterferon alfa-2a	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pegvisomant	Yes		Yes	Yes	Yes			
Pemetrexed	Yes		Yes	Yes	Yes	Yes	Yes	
Posaconazole	Yes		Yes	Yes	Yes	##	†	
Riluzole	Yes	##	Yes	Yes	Yes	Yes	Yes	
Sorafenib	Yes		Yes	Yes	Yes	##	Yes	
Tenofovir disoproxil	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Tositumomab, Iodine I-131 Tositumomab	Yes		~					
Trastuzumab	Yes		Yes	Yes	Yes	Yes	Yes	Yes
Verteporfin	Yes		Yes	Yes	Yes	Yes	Yes	
Vorinostat	Yes				‡			
Total	**64**	**20**	**58**	**58**	**49**	**30**	**39**	**19**

a See the discussion on the effects on NICE guidance and subsidy status in the absence of NICE guidance in the Discussion section.

b Funded under the Life Saving Drugs Program, which operates separately from the PBS. Imiglucerase, agalsidase alfa, agalsidase beta and laronidase were funded in 2007. Galsulfase and idursulfase gained funding in 2008, miglustat in 2009, and alglucosidase alfa in 2010.

c Subsidized beginning in August 2007.

d Fast tracked by the US FDA for treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

e Only dermal forms are listed, not ocular.

f Fast tracked by the FDA for the treatment of known or suspected cyanide poisoning.

g Fast tracked by the FDA for treatment of patent ductus arteriosis.

Aus = Australia; **lic.** = licensed; **NICE** = National Institute for Health and Clinical Excellence; **NZ** = New Zealand; **PBS** = Pharmaceutical Benefits Scheme; **PHARMAC** = Pharmaceutical Management Agency; **sub.** = subsidized; **VANF** = Department of Veterans Affairs National Formulary; **~** indicates orphan drug designation; † indicates licensed in 2008; ‡ indicates licensed in 2009; **#** indicates subsidized from 2008; **##** indicates subsidized from 2009; **###** indicates subsidized from 2010.

by the Life Saving Drugs Program in that period) and one by PHARMAC.

Discussion

The present study found the US had the highest number of innovative entities licensed and the newest licensed entities. The UK had the most licensed entities, and the NHS had the most subsidized entities, the newest subsidized entities and the highest number of subsidized innovative entities. NZ had fewer licensed and subsidized entities, older licensed and subsidized entities, and fewer licensed and subsidized innovative entities than any other country.

The present study is the first to use this newly developed method of international comparison[35] to compare access to medicines in these four countries, and the first to compare the full range of listed products by their time since first registration.

This new method examines the entire range of products listed in prescribing references, and so gives a better picture of overall access than comparing a selected subset such as newly launched products or bestselling medicines.[53,54] The large dataset (over 9000 products) creates good statistical power for detecting differences between countries. Comparing products by ATC code is more accurate than comparing active agents because it captures different formulations and indications of the same active agent. This is especially important for subsidy comparisons, as subsidy listings are usually by indication and route. Linking the time since first registration to ATC code allows comparison of how quickly countries license and subsidize new formulations and indications.

Lastly, this method includes a way of calculating the number of innovative entities licensed and subsidized in each country. Researchers have in the past considered the seriousness of the disease, the availability (or lack) of existing treatments and the effectiveness of the treatment in determining how innovative a treatment is.[55,56] The present methodology includes these factors, but also favours medicines that provide an *added* benefit over those currently in use. This is especially true of medicines listed as a 'breakthrough or substantial improvement' by the PMPRB. The criterion of added value is increasingly being used by public reimbursement agencies.[57,58] 'Breakthrough or substantial improvement' drugs are roughly equivalent to those in levels 7 and 8 (most innovative: treatment for a disease that had no previous treatment, or a new mode of treatment) on the scale used by the Austrian Medicines Evaluation Commission (HEK)[58] or Improvement of Medical Benefit Assessment (ASMR) I and II (most innovative: major therapeutic advance, significant increase in efficacy, or significant reduction in adverse effects) by the French Transparency Commission.[57] This weights the methodology towards the most innovative drugs.

The differences in licensing between the US and New Zealand is understandable given that the US spends well over three times as much as NZ per capita on pharmaceuticals.[59] As we noted previously, the VA is only one of a number of public and private health systems in the US, which provide a large pharmaceutical market. According to Danzon et al.,[54] drug manufacturers launch more products and launch these products earlier in larger markets. Danzon et al.[54] found the median delay before a drug was launched was inversely correlated with the number of launches. The US is a much more lucrative market for the launch of new products, including innovative products, prompting manufacturers to launch products first in the US. It is worth noting that by April 2010, 61 of the 65 innovative products were licensed in the UK, 57 in Australia and 50 in NZ as these countries caught up with the US.

The VANF and PBS are consistently in the middle of the four systems in terms of the number of subsidized entities, age of subsidized entities and the number of innovative entities subsidized. This is not surprising, as both systems have similar features. Both systems use positive lists of medicines, both use pharmacoeconomic evaluation in their listing decisions, and both conduct price negotiations with suppliers. Unlike PHARMAC, neither has a capped pharmaceutical budget that can never be exceeded, and both separate pharmacoeconomic considerations from price negotiation by delegating them to different bodies.

Both limit patient costs through fixed co-payments and yearly safety nets. The key difference is that the PBS covers all Australian residents, while the VANF covers a defined sector of the US population and has limited enrolment.

The wide range of health coverage in the US means that VA patients have other means of paying for drugs that are not in the VANF, such as through Medicare or private insurance. Cohen et al.[60] previously found US patients have faster and more flexible access to high-cost drugs than patients in the UK, though with higher cost sharing and more variable coverage. Similarly, US patients had faster access and more choices in coverage for top-selling pharmaceuticals than patients in the UK, France and the Netherlands, but with the drawbacks of higher cost and less evenly spread coverage.[60]

Australian patients also have other options if a medicine is not funded by the PBS. Australia uses the Life Saving Drugs Program to publicly fund expensive medicines that the PBAC has found to be clinically effective and necessary, but were not cost effective enough to be included on the PBS.[61] Research has previously shown that medicines with poor cost effectiveness are less likely to funded by the PBS than by the NHS.[62] Wonder et al.[63] also found that listings on the PBS that are likely to cause significant cost to the Australian Government were delayed compared with less expensive listings. Interestingly, our study found that the PBS reimbursed ten new innovative medicines between the end of 2007 and April 2010 (with four more newly subsidized by the Life Saving Drugs Program), whereas the VANF subsidized four new innovative medicines and PHARMAC only one. Australia therefore publicly funded 48 of the 57 innovative medicines that were licensed in Australia by April 2010. The use of two distinct sources of public funding, one for the majority of medicines and one for medicines with limited evidence of cost effectiveness, may have given Australian patients faster access to innovative medicines over this period. However, this rapid increase may not be sustainable in the current financial climate. The Australian Government has recently announced that new additions to the PBS will be deferred until 2013 in an effort to contain spending.[64]

The NHS subsidizes more entities, newer entities and more innovative entities than the three other systems. The automatic subsidy of high-cost medicines by the NHS following NICE approval is a great deal more open than the process used by the other systems. NHS patients also do not face the automatic delay while every pharmaceutical is assessed for reimbursement as in the other systems. However, not all NHS patients have access to all of the above, and access criteria may differ. Individual PCTs are expected to make decisions on a case-by-case basis when NICE guidance is not available.[65] In the systems with positive lists, there is a smaller range of available medicines, but more certainty about what treatments can be accessed, by whom and under what criteria.

It is worth noting that the UK system is undergoing major changes at the time of writing. In its 2010 white paper 'Equity and excellence: liberating the NHS',[66] the UK Government signalled a shift to value-based pricing when the current PPRS ends in 2014. Value-based pricing will base the price of each drug on the benefit it gives the NHS. The role of NICE will also change, though details have yet to be finalized.[66] It will be interesting to see how the final definition of 'value' used by the NHS compares with those used by the Canadian PMPRB, French Transparency Commission and HEK discussed above.

At the other end of the scale, NZ's PHARMAC subsidized fewer entities, subsidized older entities and subsidized fewer innovative entities than any other country. PHARMAC has the tightest constraints on its spending. PHARMAC is legally obliged to "secure for eligible people in need of pharmaceuticals, the best health outcomes that are reasonably achievable from pharmaceutical treatment and *from within the amount of funding provided*"[67] (emphasis added). This means that PHARMAC cannot, by law, ever exceed its yearly budget.[67] In order to achieve this, PHARMAC manages the Pharmaceutical Schedule, conducts pharmacoeconomic evaluations, negotiates with suppliers and manages the pharmaceutical budget. None of the other systems have one agency responsible for all these functions. This means that NZ has very strong levers

for cost containment. NZ's pharmaceutical spending has increased by only 2% annually between 1994 and 2008 (whereas overall health spending rose by 7.2% annually), while access to medicines increased.[26,28] NZ also keeps patient co-payments low, with most patients paying only $US2.2. Nevertheless, as the present study shows, the trade-off for this is fewer and older entities being subsidized than in the other systems.

Conclusion

The four single-payer systems examined differ in the number of entities subsidized, age of entities subsidized and number of innovative medicines subsidized. The NZ PHARMAC system subsidized the fewest and oldest entities, and subsidized the smallest number of innovative entities. The NHS subsidized the most entities, newest entities and most innovative entities. The trade-off between the three dimensions of access examined here and other considerations such as cost containment and evenness of patient access is one that health systems around the world have to grapple with.

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