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BRIEF REPORT

Reduction in Herpes Zoster Antiviral Use Since the Introduction of the Live-Attenuated Zoster Vaccine on Australia's National Immunisation Program: A Population-Based Study from 1994 to 2019

Sachin Phakey · Sophie L. Rogers · Anthony J. Hall · Lyndell L. Lim

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ABSTRACT

Introduction: Zostavax, the live-attenuated vaccine used to prevent herpes zoster (HZ), has been available to individuals aged 70 and 71–79 years (phased catch-up) via Australia's National Immunisation Program (NIP) since 2016. There are limited data characterising the incidence of HZ at the level of the Australian population. National prescription data for antivirals used to treat HZ may be used as a proxy for HZ incidence. We aimed to examine trends in antiviral prescriptions supplied for the treatment of HZ in Australia pre- and post-2016, and to assess whether Zostavax's inclusion on the NIP correlated with a reduction in HZ antiviral prescription rates.

Methods: Using the Australian Pharmaceutical Benefits Scheme and Repatriation Pharmaceutical Benefits Scheme prescribing data, we analysed antiviral prescriptions supplied for the treatment of HZ Australia-wide between 1994 and 2019. Annual prescription rates were calculated, and trends and changes in HZ antiviral use were explored descriptively and using Poisson models.

Results: HZ antiviral prescription rates increased 2.6-fold (160%) between 1995 and 2015 [25.4 (95% CI 25.2, 25.6) and 65.3 (95% CI 64.9, 65.6) prescriptions per 10,000 people, respectively], and then decreased 0.45-fold (55%) between 2016 and 2018 [60.9 (95% CI 60.6, 61.2) and 27.5 (95% CI 27.3, 27.9) prescriptions per 10,000 people, respectively]. The prescription rate for the antiviral famciclovir restricted specifically for treating HZ in immunocompromised individuals increased 8.5-fold (750%) between 2006 (year first listed) and 2019 [0.3 (95% CI 0.3, 0.3) and 2.5 (95% CI 2.4, 2.6) prescriptions per 10,000 people, respectively].

Conclusion: The introduction of the live-attenuated HZ vaccine on Australia's formal national vaccination program was associated with a reduction in HZ antiviral prescription rates within the Australian population. The data suggest that the introduction of Shingrix, the non-live subunit zoster vaccine, may also be associated with a similar reduction in HZ antiviral prescriptions used to treat the

S. Phakey · S. L. Rogers · L. L. Lim (✉)
Centre for Eye Research Australia, The Royal Victorian Eye and Ear Hospital, Level 7, 32 Gisborne Street, East Melbourne, VIC 3002, Australia
e-mail: limllp@unimelb.edu.au

A. J. Hall
Ophthalmology, Alfred Health, Melbourne, VIC, Australia

A. J. Hall
Department of Surgery, Monash University, Clayton, VIC, Australia

L. L. Lim
Ophthalmology, Department of Surgery, The University of Melbourne, Parkville, VIC, Australia

immunocompromised, as well as the general population, given its accepted greater efficacy over Zostavax.

Keywords: Aciclovir; Famciclovir; Herpes zoster; Immunocompromised; Immunosuppressed; Shingrix; Trends; Vaccination; Valaciclovir; Zostavax

Key Summary Points

Why carry out this study?

Zostavax is the live-attenuated herpes zoster (HZ) vaccine, which has been available via Australia's National Immunisation Program (NIP) since 2016.

With limited population-based data available, national prescription data for antivirals used in the treatment of HZ may be used as a surrogate to evaluate HZ incidence within the Australian population, and to examine whether Zostavax's inclusion on the NIP has been associated with a decrease in HZ antiviral prescription rates.

What was learned from this study?

This retrospective population-based study analysed antiviral prescriptions supplied for the treatment of HZ to all Australian residents and veterans between 1994 and 2019.

HZ antiviral prescription rates increased 2.6-fold in the period prior to the introduction of Zostavax on Australia's NIP (1995–2015), and then decreased 0.45-fold in the period following Zostavax's introduction on the NIP (2016–2018). The antiviral prescription rate for treating HZ in the immunocompromised tended to continue to increase even after the introduction of Zostavax on the NIP, increasing 8.5-fold between 2006 and 2019.

The introduction of Zostavax on Australia's NIP was associated with a reduction in HZ antiviral prescriptions in the Australian population.

The introduction of Shingrix, the non-live subunit zoster vaccine, may also be associated with a decrease in HZ antiviral prescriptions used to treat the immunocompromised, and the general population, as it has greater efficacy than Zostavax.

INTRODUCTION

Herpes zoster (HZ), commonly known as shingles, is an infective neurocutaneous disorder caused by reactivation of latent varicella-zoster virus (VZV) [1]. Primary VZV infection manifests as varicella (chickenpox). Thereafter, VZV resides latently in dorsal root or cranial nerve ganglia and can reactivate [1]. HZ typically presents as a painful vesicular dermatomal eruption [1]. Postherpetic neuralgia (PHN) is a complication of HZ involving as many as 70% of cases, characterised by chronic pain and dysaesthesia lasting for months to years [1]. HZ and its complications are a source of significant healthcare utilisation, costing the Australian health system at least AUD$32.8 million annually [2]. The incidence of HZ has been increasing, both in Australia and globally [3].

HZ may be prevented with vaccination and treated with antiviral therapy. Zostavax is a live-attenuated vaccine which, in the Shingles Prevention Study [4], a randomised controlled trial following 38,546 adults aged ≥ 60 years, reduced the incidence of HZ and PHN by 51.3% and 66.5%, respectively, over a median follow-up of 3.1 years. In Australia, the Australian Technical Advisory Group on Immunisation (ATAGI) recommends Zostavax administration for individuals aged ≥ 60 years [5]. Since

November 2016, the Australian National Immunisation Program (NIP) has provided free Zostavax vaccination for individuals aged 70 and 71–79 years (catch-up program available until 31 October 2023) [5, 6]. Others recommended to receive the vaccine, such as those aged 60–69 years and ≥ 80 years, must pay for the vaccination. Shingrix, an alternative to Zostavax, is a non-live subunit vaccine, which has increased efficacy in preventing HZ. In a randomised controlled trial of 15,411 adults aged ≥ 50 years, Shingrix vaccination provided 97.2% protection against HZ during a mean follow-up of 3.2 years [7]. Shingrix has been available for use in Australia since September 2021 via private prescription. It is not funded via the NIP [8]. Since becoming available in Australia, the ATAGI recommends Shingrix over Zostavax as the preferred zoster vaccine for adults aged ≥ 50 years [8]. Beyond vaccination, aciclovir, famciclovir and valaciclovir are HZ antiviral treatments, which reduce the severity, duration, and long-term sequelae of HZ [1].

Few data characterise the incidence of HZ at the level of the Australian population. VZV infection is notifiable in Australia, and the National Notifiable Diseases Surveillance System (NNDSS) records notifications of both varicella and HZ [9]; yet, HZ data are limited. VZV infection is not notifiable in New South Wales, Australia's largest state, and, moreover, a significant proportion of VZV infections reported to the NNDSS are unspecified as either varicella or HZ [9]. Of the 85,870 VZV notifications to the NNDSS between 2016 and 2018, 51.5% were unspecified [9]. Registry data may also be used to interrogate HZ incidence in Australia. However, enrolled participants may not necessarily be representative of the wider Australian population, limiting the generalisability of the findings. Conversely, antiviral prescriptions used to treat HZ are a stable data source available at a national level to evaluate HZ incidence within the Australian population [10].

Using national medication prescription data, we aimed to explore trends in antiviral prescriptions supplied for the treatment of HZ in Australia from 1994 to 2019, and to examine whether Zostavax's inclusion on the NIP in 2016 was associated with a reduction in HZ antiviral prescription rates.

METHODS

Study Design

We performed a retrospective population-based time-trend analysis from 1 October 1994 to 31 December 2019 inclusive, assessing trends and changes in HZ antiviral prescription supply rates recorded by the Australian Pharmaceutical Benefits Scheme (PBS) and Repatriation Pharmaceutical Benefits Scheme (RPBS).

Database and Antiviral Medications Ascertained

The Australian PBS and RPBS are components of Australia's healthcare system, contributing to and facilitating universal healthcare. The PBS and RPBS list all medications available to Australian residents and veterans, respectively, for a subsidised price [11]. PBS/RPBS item numbers are used to denote different medication formulations, indications and/or restrictions in their prescription. PBS- and RPBS-subsidised medications are dispensed by community pharmacies, private hospitals and some public hospitals [11]. Medication supply data recorded by the PBS and RPBS are highly representative of medication use by the Australian population overall. Non-PBS/RPBS medications are not subsidised by the Australian Government, and individuals must pay full price using a private prescription.

The PBS/RPBS Schedule lists four antiviral medications for the treatment of HZ: aciclovir (PBS/RPBS item no. 1052J), valaciclovir (item no. 8064K) and famciclovir (item no. 8002E) for HZ treatment in immunocompetent individuals, and famciclovir (item no. 8897G), which is restricted for HZ treatment in immunocompromised individuals [12]. The PBS/RPBS Schedule does not detail specific immunocompromising conditions which qualify for treatment with famciclovir item no. 8897G. Data reports detailing prescriptions supplied for specific PBS/RPBS item numbers are made

publicly available by the Department of Health [13]. Using this resource, we examined the number of prescriptions supplied for the four HZ antivirals in all Australian states and territories, in each calendar month between 1 October 1994 (or year available on the PBS/RPBS) to 31 December 2019 inclusive. The data extracted indicate that aciclovir (item no. 1052J) was listed on the PBS/RPBS in October 1994, valaciclovir (item no. 8064K) in August 1996, famciclovir (item no. 8002E) in November 1995, and famciclovir (item no. 8897G) in May 2006. Changes in HZ antiviral prescriptions supplied were used as a proxy for changes in HZ incidence. Prescriptions supplied for the four HZ antivirals via the PBS/RPBS are likely to represent incident HZ cases because: firstly, these item numbers are restricted in their use and cannot be used for non-zoster indications, with different PBS/RPBS item numbers used for non-zoster indications (for example, genital herpes due to herpes simplex virus) [11, 12]; secondly, treatment of cutaneous zoster must be administered within 72 h of rash onset [12]; and thirdly, chronic sequelae of zoster (such as PHN) are unlikely to be treated with antiviral therapy. Data were retrospectively extracted in April 2020. The study was approved by The Royal Victorian Eye and Ear Hospital Human Research Ethics Committee (reference, 18/1402HL).

Statistical Analysis

Annual prescription rates (prescriptions per 10,000 people) were calculated, and the total number of prescriptions supplied in each calendar year in all Australian states and territories combined were divided by the Australian Bureau of Statistics' annual Australian estimated resident population for that year [14]. Annual antiviral prescription rates were calculated for the four antiviral PBS/RPBS item numbers separately. Annual total HZ antiviral prescription rates were also calculated, after summing the total number of prescriptions supplied for the four antiviral PBS/RPBS item numbers. Analysis of prescription rates, rather than the number of HZ antiviral prescriptions alone, intended to control for potential confounding due to an increasing Australian population with time.

Trends and changes in HZ antiviral prescription rates in the Australian population were explored descriptively. Poisson models were used to calculate prescription rates and their 95% confidence intervals (CI). Prescription rates were plotted over time between 1994 (or when first available on the PBS/RPBS) and 2019. Data analyses were conducted using Stata IC 15.1 Data Analysis and Statistical Software (StataCorp, College Station, TX, USA).

RESULTS

Number of Antiviral Prescriptions Supplied to Treat HZ

Between 1994 (or year of first listing on the PBS/RPBS) and 2019, there were 280,353 aciclovir (item no. 1052J), 781,359 valaciclovir (item no. 8064K), 1,037,976 famciclovir (item no. 8002E) and 45,653 famciclovir (item no. 8897G) prescriptions supplied for the treatment of HZ in Australia (Table 1). Of all Australian states and territories, the majority of prescriptions were supplied in New South Wales for all four antivirals [aciclovir, 95,988 prescriptions (34.2%); valaciclovir, 265,683 prescriptions (34.0%), famciclovir item no. 8002E, 348,670 prescriptions (33.6%), and famciclovir item no. 8897G, 13,459 prescriptions (29.5%)].

Prescription Rate of Antiviral Medications Used to Treat HZ

Overall, the total prescription rate for all antivirals used to treat HZ in Australia increased 2.6-fold (160%) between 1995 and 2015, from 25.4 (95% CI 25.2, 25.6) to 65.3 (95% CI 64.9, 65.6) prescriptions per 10,000 people, respectively (Table 2; Fig. 1). A decreased prescription rate [48.3 (95% CI 48.0, 48.6) prescriptions per 10,000 people] was observed in 2013, relative to 2012 [53.5 (95% CI 53.1, 53.8) prescriptions per 10,000 people]. The total antiviral prescription rate decreased 0.45-fold (55%) between 2016 and 2018, from 60.9 (95% CI 60.6, 61.2) to 27.5

Table 1 Number of antiviral prescriptions supplied for the treatment of herpes zoster in all Australian states and territories from 1994 (or when first available on the Pharmaceutical Benefits Scheme) to 2019, by antiviral medication

Year	NSW	VIC	QLD	SA	WA	TAS	ACT	NT	Australia total
Aciclovir (item no. 1052J)									
1994	862	489	282	102	115	42	29	4	1925
1995	16,613	11,433	7735	3669	3493	1217	616	177	44,953
1996	11,947	7168	5661	2495	2710	797	455	156	31,389
1997	6831	4141	3317	1231	1637	506	244	94	18,001
1998	4732	2740	2218	830	1177	361	233	83	12,374
1999	4320	2399	1975	655	1118	379	163	122	11,131
2000	3813	2285	1823	481	996	335	125	80	9938
2001	3214	1925	1567	519	913	290	134	90	8652
2002	2698	1733	1267	387	724	324	84	42	7259
2003	2485	1719	1162	374	644	268	83	64	6799
2004	2335	1746	1262	401	692	240	66	41	6783
2005	2408	1897	1498	390	661	285	80	48	7267
2006	2477	1890	1452	356	672	273	97	43	7260
2007	2240	1969	1462	332	763	289	105	43	7203
2008	2146	1897	1454	384	717	315	93	41	7047
2009	2248	1902	1514	465	709	262	72	46	7218
2010	2266	1928	1637	397	817	239	83	52	7419
2011	2356	2193	1639	489	881	272	103	70	8003
2012	2609	2690	1913	545	1106	295	146	79	9383
2013	2495	2152	2106	572	1049	282	132	73	8861
2014	3221	3224	1943	526	1555	288	164	110	11,031
2015	3686	3587	2246	680	1519	345	158	125	12,346
2016	2750	2827	1943	546	1390	228	138	95	9917
2017	2132	1986	1483	476	1134	198	94	74	7577
2018	1618	1448	1099	357	772	142	77	31	5544
2019	1486	1234	981	323	782	154	79	34	5073
Valaciclovir (item no. 8064K)									
1996	521	224	308	129	119	55	25	1	1382
1997	4383	2267	2442	1104	809	285	183	34	11,507
1998	6759	3866	4101	1590	1162	368	299	56	18,201
1999	7404	4613	4560	1601	1504	376	317	61	20,436

Table 1 continued

Year	NSW	VIC	QLD	SA	WA	TAS	ACT	NT	Australia total
2000	8744	5345	5691	1731	1751	461	498	64	24,285
2001	9389	5854	6332	1973	2076	483	512	115	26,734
2002	9868	6043	6492	2045	2280	473	593	157	27,951
2003	9890	6485	6612	2090	2419	503	521	136	28,656
2004	10,626	6527	7287	2297	2675	582	634	157	30,785
2005	11,070	6666	7383	2393	2847	650	640	172	31,821
2006	10,996	6643	7657	2223	2921	572	660	114	31,786
2007	10,884	6593	7915	2209	2949	537	674	117	31,878
2008	10,754	6238	7736	1990	2862	630	606	113	30,929
2009	11,467	6756	8410	2234	3072	613	655	182	33,389
2010	11,986	7424	9081	2279	3290	702	659	201	35,622
2011	12,637	8246	9906	2407	3712	724	777	244	38,653
2012	15,050	9518	11,571	2745	4416	805	881	262	45,248
2013	13,166	7852	12,429	2675	3835	797	777	256	41,787
2014	18,945	11,705	12,902	2715	5898	834	1174	287	54,460
2015	20,637	12,875	15,617	3306	6144	1025	1208	352	61,164
2016	19,784	12,661	15,793	3267	6052	1022	1161	383	60,123
2017	11,737	7778	9897	1866	3785	792	568	177	36,600
2018	8937	5613	7439	1512	2768	621	358	111	27,359
2019	10,049	6378	8377	1613	2937	674	403	172	30,603
Famciclovir (item no. 8002E)									
1995	284	266	181	88	63	28	9	0	919
1996	6036	5726	3456	1528	1285	484	266	61	18,842
1997	8874	7627	4874	2183	2206	661	372	99	26,896
1998	9534	8425	4872	2526	2496	831	360	126	29,170
1999	10,288	8633	4834	2867	2757	858	427	147	30,811
2000	10,359	8652	4797	2779	2640	889	359	122	30,597
2001	11,145	9467	5044	3064	2846	927	397	119	33,009
2002	11,873	9454	5573	3082	3042	988	406	104	34,522
2003	11,876	9815	6063	3050	3092	937	466	95	35,394
2004	12,557	10,062	5942	2948	3123	979	436	111	36,158
2005	13,406	10,389	6314	3200	3000	947	385	103	37,744

Table 1 continued

Year	NSW	VIC	QLD	SA	WA	TAS	ACT	NT	Australia total
2006	13,481	11,237	6701	3239	3123	954	461	100	39,296
2007	14,164	11,875	7221	3508	3267	1000	523	108	41,666
2008	15,337	12,121	8017	3613	3659	1128	608	123	44,606
2009	16,973	13,360	8535	4283	3693	1196	756	212	49,008
2010	17,239	14,352	8925	4313	4189	1335	754	136	51,243
2011	18,477	15,191	9608	4522	4318	1345	776	174	54,411
2012	21,371	17,834	11,094	5251	5137	1626	888	153	63,354
2013	18,377	15,307	11,489	5648	4210	1643	794	213	57,681
2014	24,644	21,887	11,491	5624	6362	1806	1088	235	73,137
2015	25,621	22,236	12,993	6601	6020	2068	1197	196	76,932
2016	23,363	20,477	12,964	6538	5623	2036	1021	201	72,223
2017	13,556	11,276	7032	3865	3236	1144	510	113	40,732
2018	10,093	8974	5333	3203	2270	1002	258	53	31,186
2019	9742	7982	4662	2853	2054	854	241	51	28,439
Famciclovir (item no. 8897G)									
2006	203	170	94	71	37	18	9	2	604
2007	394	321	241	147	69	54	14	5	1245
2008	390	343	242	137	78	41	15	11	1257
2009	495	379	347	183	100	39	18	9	1570
2010	540	463	335	221	141	50	29	14	1793
2011	719	649	515	235	178	68	35	18	2417
2012	982	948	684	328	246	110	40	14	3352
2013	1049	886	685	418	246	114	30	18	3446
2014	1412	1327	823	484	360	144	57	23	4630
2015	1409	1332	883	557	345	142	41	24	4733
2016	1265	1473	897	467	360	113	83	28	4686
2017	1389	1383	869	619	419	153	63	31	4926
2018	1314	1341	822	628	361	147	46	15	4674
2019	1898	1710	1174	725	511	190	81	31	6320

ACT Australian Capital Territory, *NSW* New South Wales, *NT* Northern Territory, *QLD* Queensland, *SA* South Australia, *TAS* Tasmania, *VIC* Victoria, *WA* Western Australia

Table 2 Total number of antiviral prescriptions supplied (all antiviral medications) and their prescription rates for the treatment of herpes zoster in Australia from 1994 to 2019

Year	Prescriptions supplied	Population in Australia[a]	Prescription rate (95% CI)[b]
1994	1925	17,843,300	1.1 (1.0, 1.1)
1995	45,872	18,054,000	25.4 (25.2, 25.6)
1996	51,613	18,289,100	28.2 (28.0, 28.5)
1997	56,404	18,532,200	30.4 (30.2, 30.7)
1998	59,745	18,751,000	31.9 (31.6, 32.1)
1999	62,378	18,966,800	32.9 (32.6, 33.1)
2000	64,820	19,157,000	33.8 (33.6, 34.1)
2001	68,395	19,386,700	35.3 (35.0, 35.5)
2002	69,732	19,707,200	35.4 (35.1, 35.6)
2003	70,849	19,881,500	35.6 (35.4, 35.9)
2004	73,726	20,111,300	36.7 (36.4, 36.9)
2005	76,832	20,328,600	37.8 (37.5, 38.1)
2006	78,946	20,605,500	38.3 (38.0, 38.6)
2007	81,992	21,017,200	39.0 (38.7, 39.3)
2008	83,839	21,374,000	39.2 (39.0, 39.5)
2009	91,185	21,875,000	41.7 (41.4, 42.0)
2010	96,077	22,342,000	43.0 (42.7, 43.3)
2011	103,484	22,620,600	45.7 (45.5, 46.0)
2012	121,337	22,683,600	53.5 (53.1, 53.8)
2013	111,775	23,130,900	48.3 (48.0, 48.6)
2014	143,258	23,490,700	61.0 (60.7, 61.3)
2015	155,175	23,781,200	65.3 (64.9, 65.6)
2016	146,949	24,127,200	60.9 (60.6, 61.2)
2017	89,835	24,598,900	36.5 (36.3, 36.8)
2018	68,763	24,992,400	27.5 (27.3, 27.9)
2019	70,435	25,364,300	27.8 (27.6, 28.0)

CI confidence interval

[a]Estimated resident population in Australia (Australian Bureau of Statistics) [14]

[b]Data are reported as prescriptions per 10,000 people

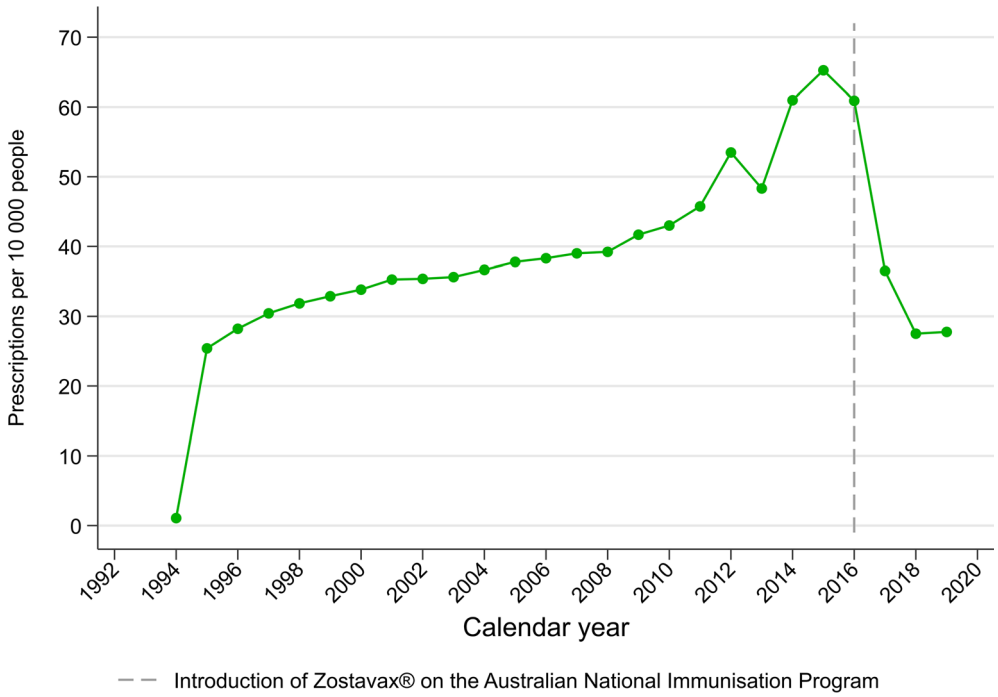

Fig. 1 Total prescription rate for all antivirals used to treat HZ per 10,000 people in Australia from 1994 (or when first listed on the Pharmaceutical Benefits Scheme) to 2019

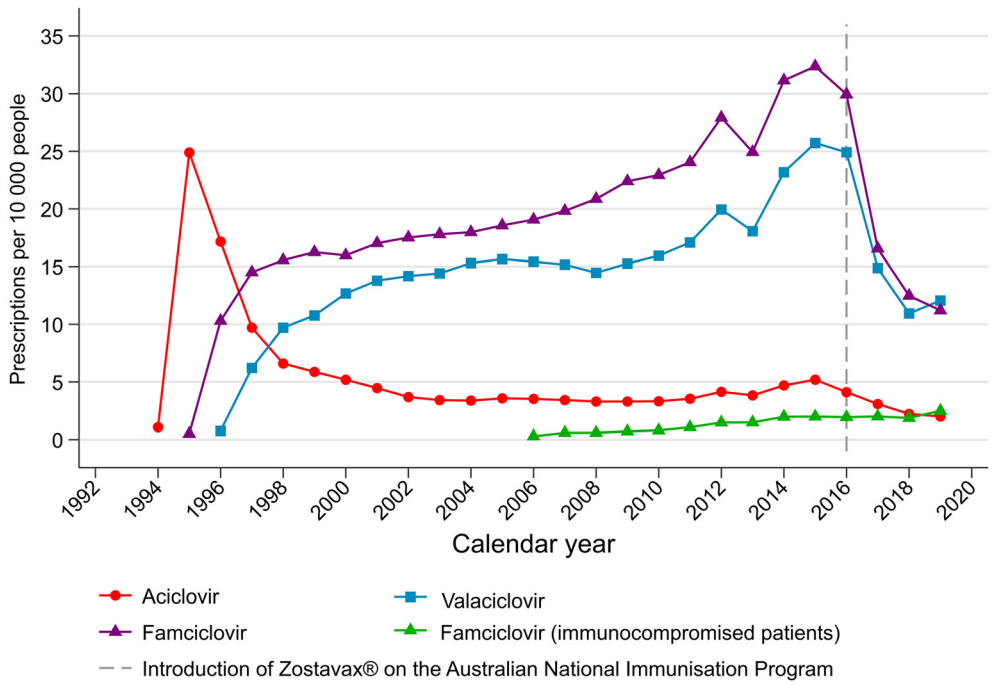

Fig. 2 Aciclovir, famciclovir and valaciclovir antiviral prescription rates per 10,000 people in Australia from 1994 (or when first listed on the Pharmaceutical Benefits Scheme) to 2019

Table 3 Number of antiviral prescriptions supplied and their prescription rates for the treatment of herpes zoster in Australia from 1994 (or when first available on the Pharmaceutical Benefits Scheme) to 2019, by antiviral medication

Year	Prescriptions supplied	Population in Australia[a]	Prescription rate (95% CI)[b]
Aciclovir (item no. 1052J)			
1994	1925	17,843,300	1.1 (1.0, 1.1)
1995	44,953	18,054,000	24.9 (24.7, 25.1)
1996	31,389	18,289,100	17.2 (17.0, 17.4)
1997	18,001	18,532,200	9.7 (9.6, 9.9)
1998	12,374	18,751,000	6.6 (6.5, 6.7)
1999	11,131	18,966,800	5.9 (5.8, 6.0)
2000	9938	19,157,000	5.2 (5.1, 5.3)
2001	8652	19,386,700	4.5 (4.4, 4.6)
2002	7259	19,707,200	3.7 (3.6, 3.8)
2003	6799	19,881,500	3.4 (3.3, 3.5)
2004	6783	20,111,300	3.4 (3.3, 3.5)
2005	7267	20,328,600	3.6 (3.5, 3.7)
2006	7260	20,605,500	3.5 (3.4, 3.6)
2007	7203	21,017,200	3.4 (3.3, 3.5)
2008	7047	21,374,000	3.3 (3.2, 3.4)
2009	7218	21,875,000	3.3 (3.2, 3.4)
2010	7419	22,342,000	3.3 (3.2, 3.4)
2011	8003	22,620,600	3.5 (3.5, 3.6)
2012	9383	22,683,600	4.1 (4.1, 4.2)
2013	8861	23,130,900	3.8 (3.8, 3.9)
2014	11,031	23,490,700	4.7 (4.6, 4.8)
2015	12,346	23,781,200	5.2 (5.1, 5.3)
2016	9917	24,127,200	4.1 (4.0, 4.2)
2017	7577	24,598,900	3.1 (3.0, 3.2)
2018	5544	24,992,400	2.2 (2.2, 2.3)
2019	5073	25,364,300	2.0 (1.9, 2.1)
Valaciclovir (item no. 8064K)			
1996	1382	18,289,100	0.8 (0.7, 0.8)
1997	11,507	18,532,200	6.2 (6.1, 6.3)
1998	18,201	18,751,000	9.7 (9.6, 9.8)
1999	20,436	18,966,800	10.8 (10.6, 10.9)
2000	24,285	19,157,000	12.7 (12.5, 12.8)
2001	26,734	19,386,700	13.8 (13.6, 14.0)
2002	27,951	19,707,200	14.2 (14.0, 14.4)
2003	28,656	19,881,500	14.4 (14.2, 14.6)
2004	30,785	20,111,300	15.3 (15.1, 15.5)
2005	31,821	20,328,600	15.7 (15.5, 15.8)
2006	31,786	20,605,500	15.4 (15.3, 15.6)
2007	31,878	21,017,200	15.2 (15.0, 15.3)
2008	30,929	21,374,000	14.5 (14.3, 14.6)
2009	33,389	21,875,000	15.3 (15.1, 15.4)
2010	35,622	22,342,000	15.9 (15.8, 16.1)
2011	38,653	22,620,600	17.1 (16.9, 17.3)
2012	45,248	22,683,600	19.9 (19.8, 20.1)
2013	41,787	23,130,900	18.1 (17.9, 18.2)
2014	54,460	23,490,700	23.2 (23.0, 23.4)
2015	61,164	23,781,200	25.7 (25.5, 25.9)
2016	60,123	24,127,200	24.9 (24.7, 25.1)
2017	36,600	24,598,900	14.9 (14.7, 15.0)
2018	27,359	24,992,400	10.9 (10.8, 11.1)
2019	30,603	25,364,300	12.1 (11.9, 12.2)
Famciclovir (item no. 8002E)			
1995	919	18,054,000	0.5 (0.5, 0.5)
1996	18,842	18,289,100	10.3 (10.2, 10.5)
1997	26,896	18,532,200	14.5 (14.3, 14.7)
1998	29,170	18,751,000	15.6 (15.4, 15.7)
1999	30,811	18,966,800	16.2 (16.1, 16.4)
2000	30,597	19,157,000	16.0 (15.8, 16.2)
2001	33,009	19,386,700	17.0 (16.8, 17.2)
2002	34,522	19,707,200	17.5 (17.3, 17.7)

Table 3 continued

Year	Prescriptions supplied	Population in Australia[a]	Prescription rate (95% CI)[b]
2003	35,394	19,881,500	17.8 (17.6, 18.0)
2004	36,158	20,111,300	18.0 (17.8, 18.2)
2005	37,744	20,328,600	18.6 (18.4, 18.8)
2006	39,296	20,605,500	19.1 (18.9, 19.3)
2007	41,666	21,017,200	19.8 (19.6, 20.0)
2008	44,606	21,374,000	20.9 (20.7, 21.1)
2009	49,008	21,875,000	22.4 (22.2, 22.6)
2010	51,243	22,342,000	22.9 (22.7, 23.1)
2011	54,411	22,620,600	24.1 (23.9, 24.3)
2012	63,354	22,683,600	27.9 (27.7, 28.1)
2013	57,681	23,130,900	24.9 (24.7, 25.1)
2014	73,137	23,490,700	31.1 (30.9, 31.4)
2015	76,932	23,781,200	32.3 (32.1, 32.6)
2016	72,223	24,127,200	29.9 (29.7, 30.2)
2017	40,732	24,598,900	16.6 (16.4, 16.7)
2018	31,186	24,992,400	12.5 (12.3, 12.6)
2019	28,439	25,364,300	11.2 (11.1, 11.3)
Famciclovir (item no. 8897G)			
2006	604	20,605,500	0.3 (0.3, 0.3)
2007	1245	21,017,200	0.6 (0.6, 0.6)
2008	1257	21,374,000	0.6 (0.6, 0.6)
2009	1570	21,875,000	0.7 (0.7, 0.8)
2010	1793	22,342,000	0.8 (0.8, 0.8)
2011	2417	22,620,600	1.1 (1.0, 1.1)
2012	3352	22,683,600	1.5 (1.4, 1.5)
2013	3446	23,130,900	1.5 (1.4, 1.5)
2014	4630	23,490,700	2.0 (1.9, 2.0)
2015	4733	23,781,200	2.0 (1.9, 2.0)
2016	4686	24,127,200	1.9 (1.9, 2.0)
2017	4926	24,598,900	2.0 (1.9, 2.1)
2018	4674	24,992,400	1.9 (1.8, 1.9)
2019	6320	25,364,300	2.5 (2.4, 2.6)

CI confidence interval

[a]Estimated resident population in Australia (Australian Bureau of Statistics) [14]

[b]Data are reported as prescriptions per 10,000 people

(95% CI 27.3, 27.9) prescriptions per 10,000 people, respectively. 2018 and 2019 antiviral prescription rates were similar.

Prescription Rates of Famciclovir and Valaciclovir for the Treatment of HZ

Since their listing on the PBS/RPBS in 1994 and 1995, prescription rates for famciclovir and valaciclovir, respectively, tended to steadily increase annually until 2015 (Fig. 2), with 2013 prescription rates being the exception. Between 1998 and 2015, valaciclovir (item no. 8064K) and famciclovir (item no. 8897G) prescription rates approximately doubled, from 9.7 (95% CI 9.6, 9.8) to 25.7 (95% CI 25.5, 25.9), and from 15.6 (95% CI 15.4, 15.7) to 32.3 (95% CI 32.1, 32.6) prescriptions per 10,000 people, respectively (Table 3). Between 2016 and 2018, valaciclovir and famciclovir prescription rates then decreased, with 2018 prescription rates [10.9 (95% CI 10.8, 11.1) and 12.5 (95% CI 12.3, 12.6) prescriptions per 10,000 people, respectively] approximately one-third of 2015 prescription rates [25.7 (95% CI 25.5, 25.9) and 32.3 (95% CI 32.1, 32.6) prescriptions per 10,000 people, respectively]. The valaciclovir prescription rate increased 1.1-fold (10%) between 2018 and 2019 [12.1 (95% CI 11.9, 12.2) prescriptions per 10,000 people].

Prescription Rate of Aciclovir for the Treatment of HZ

Following its availability on the PBS/RPBS in 1994, the aciclovir prescription rate peaked at 24.9 (95% CI 24.7, 25.1) prescriptions per

10,000 people in 1995 (Table 3; Fig. 2). Thereafter, the aciclovir prescription rate decreased to one-fifth of this peak rate by 2000 [5.2 (95% CI 5.1, 5.3) prescriptions per 10,000 people]. The aciclovir prescription rate remained largely stable between 2003 and 2011 (ranging from 3.3 to 3.6 prescriptions per 10,000 people), tended to increase between 2012 and 2015 [rising from 4.1 (95% CI 4.1, 4.2) to 5.2 (95% CI 5.1, 5.3) prescriptions per 10,000 people, respectively], and then decreased between 2016 and 2019 [falling from 4.1 (95% CI 4.0, 4.2) to 2.0 (95% CI 1.9, 2.1] prescriptions per 10,000 people, respectively].

Prescription Rate of Famciclovir for the Treatment of HZ in the Immunocompromised

Annual prescription rates for famciclovir (item no. 8897G) restricted for treating HZ in immunocompromised patients have increased 8.5-fold (750%) between 2006 (year first available) and 2019 [0.3 (95% CI 0.3, 0.3) and 2.5 (95% CI 2.4, 2.6) prescriptions per 10,000 people, respectively] (Table 3; Fig. 2). The famciclovir prescription rate tended to continue to increase even after the introduction of Zostavax on the NIP between 2016 and 2019 [rising from 1.9 (95% CI 1.9, 2.0) to 2.5 (95% CI 2.4, 2.6) prescriptions per 10,000 people, respectively].

DISCUSSION

In this Australian population-based study with over 25 years of retrospective observation, we explored trends in national HZ antiviral prescription rates over time as a surrogate marker for changes in HZ incidence. The introduction of Zostavax on Australia's formal national vaccination program was associated with a reduction in prescription rates for antiviral medications used to treat HZ. Prescription rates increased 2.6-fold in the period prior to the introduction of Zostavax on Australia's NIP between 1995 and 2015, and then decreased 0.45-fold following its introduction on Australia's NIP between 2016 and 2018. Although Zostavax was available privately in Australia prior to its listing on the NIP from 2008 [15], uptake among those at risk was low. In October 2016, 197 doses of Zostavax were administered to those aged 70 years [15]. In contrast, an average of 4,500 doses were administered each month to those aged 70 years in the first five months of its listing on the NIP [15].

Other potential factors may have influenced HZ antiviral prescription rates with time, and contributed to the decrease observed in 2016 onwards. These include changes to the age distribution, varicella vaccination coverage, and lifestyle, healthcare access and health-seeking behaviour of the Australian population. There were an estimated 1,553,615 and 1,792,241 people aged 70–79 years in Australia at 30 June in 2016 and 2019 [14], accounting for 6.4% and 7.1% of the total population, respectively. This suggests there was no confounding marked increase in the vaccine-eligible population during the study period. Moreover, given that Australia's population is ageing, and because increasing age is associated with increased HZ risk, it could have been expected that HZ antiviral prescriptions would continue to increase over time, including between 2016 and 2019, yet this was not observed. Similarly, varicella vaccination uptake has remained largely unchanged, with Australian Immunisation Register coverage estimates for children aged 24 months in 2016 and 2019 ranging between 91.2–92.8% and 92.7–93.6%, respectively [16]. This provides reassurance that the correlation between the inclusion of Zostavax on the NIP and the sharp decline in HZ antiviral prescriptions observed in 2016 onwards is legitimate.

Our study supports the findings of the only two other studies investigating HZ incidence in the post-Zostavax era in Australia [17, 18]. The first also examined trends in HZ antiviral prescriptions over time as a surrogate for HZ incidence, recording a 13.6% mean decrease in antiviral prescriptions in individuals aged 70–79 years in the two years following the introduction of Zostavax [17]. This was also preceded by a ten-year period of increasing prescription rates. While the authors also used the PBS database to ascertain HZ antiviral prescriptions, their data were limited to a 10% sample of claims. RPBS data were also not included. The

second study analysed the diagnostic codes and vaccination records for a 25% random sample from the MedicineInsight Australian general practice registry, comparing the incidence of HZ in the vaccinated and unvaccinated in the two years following the introduction of Zostavax on the NIP [18]. In 2017 and 2018, Zostavax vaccination reduced the risk of HZ by 64% and 48%, respectively. The representativeness of the findings may be reduced, given the registry design and proportioned sample used. The incidence of HZ in the pre-Zostavax era was not explored.

HZ incidence may be reduced further in Australia. Firstly, HZ vaccination coverage can be improved. Australian Immunisation Register (AIR) data reports decreased Zostavax uptake rates of 33.9% and 25.8% in 70-year-olds and 71–79-year-olds respectively between 2016 and 2018 [15]. This may be an underestimation due to underreporting to the AIR [15]. Coverage is significantly lower compared with England, where there is a similarly structured, publicly-funded vaccination program which began in 2013. In 2015–2016, Zostavax uptakes rates in England were 54.9% and 55.5% in 70-year-olds (routine cohort) and 71–79-year-olds (catch-up cohort), respectively [19]. Our study findings demonstrating equivalent 2018 and 2019 HZ antiviral prescription rates and an increase in the valaciclovir prescription rate by 10% between 2018 and 2019 may suggest that HZ rates have stabilised in Australia, following the decrease in prescriptions observed with the introduction of Zostavax. Australian health professionals and vaccination providers are encouraged to continue to vaccinate at-risk individuals as per the NIP, and to record these data with the AIR. Secondly, increasing use of Shingrix, the new HZ vaccine that is more effective than Zostavax, will likely also assist in decreasing HZ incidence. Health policymakers could consider making Shingrix available via the NIP to increase its uptake among those at risk. Furthermore, as a non-live vaccine, Shingrix may possibly be used in the immunosuppressed. We found an 8.5-fold increase in the prescription rate of famciclovir used to treat HZ in the immunocompromised between 2006 and 2019, which may reflect increasing incidence of HZ in the immunocompromised. It should be noted that Zostavax, being a live vaccine, is contraindicated for people who are currently or recently immunocompromised due to disease or medical treatment [5].

There are limitations to this study. Firstly, our results are limited by the quality of the data. The aggregate-level data extracted were not stratified by age or sex, preventing stratification or adjustment by these potential predictors when exploring temporal trends in HZ incidence. This also limits our ability to determine whether HZ antiviral prescriptions supplied following the introduction of Zostavax on the NIP were among unvaccinated younger Australians or occurring among older at-risk Australians who may have already been vaccinated, potentially indicating "vaccine failure". Secondly, antiviral prescribing data may imperfectly characterise HZ incidence. Since antiviral prescription relies on healthcare-seeking behaviour, it is possible that milder HZ cases may not seek medical care, leading to potential under-ascertainment. Conversely, the use of antiviral prescription data may overestimate HZ rates due to prescriptions supplied for zoster prophylaxis, rashes erroneously diagnosed as HZ, and patients potentially requiring more than one course of HZ treatment. However, these prescribing behaviours would likely not have changed differentially over the study period so should not change the overall results of our study. Changes in antiviral prescribing patterns may also confound analysis of antiviral usage. Following the introduction of famciclovir and valaciclovir on the PBS/RPBS in 1995 and 1996, respectively, aciclovir prescription rates decreased 0.21-fold (79%) between 1995 and 2000, while famciclovir and valaciclovir prescription rates increased. This may reflect prescribers' preference to use famciclovir and valaciclovir when treating HZ compared to aciclovir. Famciclovir and valaciclovir are administered less frequently. Similarly, antiviral medication shortages may lead to a reduction in prescriptions supplied. While there were shortages of aciclovir, valaciclovir and famciclovir in Australia reported by the Therapeutics Good Administration during the study period, to our knowledge, these only occurred in 2019, were

intermittent, and only ever had an impact rating of low or medium (never high or critical) [20]. Although it is possible that changes in prescription rates could be attributed to variation in prescribing behaviours, notably, prescription rates for all antivirals used to treat HZ in the immunocompetent otherwise trended together throughout the study period, including in the post-Zostavax period. Reassuringly, the overall rate and the steady increase seen in prescription rates prior to the introduction of zoster vaccination mirrors the overall incidence and the steady increase in HZ incidence seen in other studies in similar populations [21, 22]. Furthermore, the use of HZ antiviral prescription data as a surrogate marker for HZ incidence has been previously validated in Australia by comparison with the Bettering the Evaluation and Care of Health general practice database [3]. Thirdly, the ecological approach of this study limits our ability to imply causation, and that the reduction in HZ antiviral rates observed within the Australian population is entirely attributable to the introduction of Zostavax. Although unmeasured confounding variables at the individual and/or population levels may possibly account for some of the reduction we observed, the marked decrease in HZ antiviral prescriptions observed immediately following the introduction of Zostavax on the NIP gives confidence to our findings of an association.

This study also has several strengths. This was a population-based study using data from two national data sources: the PBS and RPBS. Since medication supply data recorded by the PBS and RPBS are reflective of medication use by the Australian population overall [11], the findings of this study are representative of the Australian population, increasing external validity. Additionally, our analysis included ≥ 25 years of retrospective observation. Antiviral trends observed are less likely to be artefactual. Furthermore, because the PBS/RPBS data interrogated were for antivirals restricted specifically for treating HZ and within 72 h, this increases our confidence in using antiviral prescription data as a surrogate for incident HZ cases.

CONCLUSION

The introduction of Zostavax on the Australian NIP in 2016 coincided with a marked reduction in HZ antiviral prescription rates within the Australian population. This was preceded by a >20-year period, during which HZ antiviral prescriptions tended to steadily increase. The recent availability of Shingrix in Australia may lead to a further reduction in HZ antiviral prescriptions, especially as it is the preferred vaccine for those aged >50 years and the immunocompromised. However, Shingrix's potential benefit may be limited if it remains accessible via private prescription only and not via Australia's NIP.

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Research Ethics Committee (HREC) approved the study (reference, 18/1402HL). The use of informed consent was waived by the HREC as the study was a retrospective analysis of anonymised medication prescription data. This study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments.

Data Availability. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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