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Estimated health and economic impact of using high-dose influenza vaccine on respiratory and circulatory plus respiratory hospitalizations of older adults in Australia

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ABSTRACT

Background: Standard dose influenza vaccine provides moderate protection from infection, but with lower effectiveness among the elderly. High dose and adjuvanted vaccines (HD-TIV and aTIV) were developed to address this. This study aims to estimate the incremental health and economic impact of using HD-TIV (high dose trivalent vaccine) instead of aTIV (adjuvanted trivalent vaccine) on respiratory and circulatory plus respiratory hospitalizations of older people (≥65 years) in Australia.

Methods: This is a modelling study comparing predicted hospitalization outcomes in people receiving HD-TIV or aTIV during an average influenza season in Australia. Hospitalization records of Australian adults ≥65 years of age from 01 April to 30 November during 15 influenza seasons (2002–2017 excluding 2009, which was a pandemic) were extracted from the Australian Institute of Health and Welfare [AIHW] and used to calculate hospitalisation rates during an average season. Relative vaccine effectiveness data for aTIV and HD-TIV were used to estimate morbidity burden related to influenza.

Results: Between 2002 and 2017, the average respiratory hospitalization rate among older people during influenza season (April-November) was 3,445/100,000 population-seasons, with an average cost of AU$ 7,175 per admission. The average circulatory plus respiratory hospitalization rate among older Australian people during that time was 10,393/100,000 population-seasons, with an average cost of AU$ 7829 per admission. For older Australians, HD-TIV may avert an additional 6,315–9,410 respiratory admissions each year, with an incremental healthcare cost saving of AU$ 15.9–38.2 million per year compared to aTIV. Similar results were also noted for circulatory plus respiratory hospitalizations.

Conclusions: From the modelled estimations, HD-TIV was associated with less economic burden and fewer respiratory, and circulatory plus respiratory hospitalizations than aTIV for older Australians.

1. Introduction

Influenza is a global disease, with epidemics occurring mainly in winter in temperate areas and perennially in tropical climates [1]. Due to age-related decline in immune function and increased comorbidities [2], adults 65 years of age and older are at increased risk of influenza

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infection and associated complications, and show a poorer response to vaccination compared with younger adults [2,3]. A recent modelling study demonstrated that influenza disproportionately burdens older adults, with nearly five times the risk of death in those ≥75 years of age compared with those 65–74 years of age [4]. In addition, older individuals have higher rates of influenza-attributable emergency department visits, as well as intensive care unit attendance [5,6].

There is evidence that influenza-associated excess mortality may be due to other chronic health conditions, which can be exacerbated or precipitated by influenza [7,8]. Influenza infections are associated with increased hospitalizations for cerebrovascular disease in adults aged 75 and over and ischemic heart disease in adults aged 40–64 and 75 and over [9,10]. A retrospective study in the USA showed that, over 7 years, emergency department visits for influenza-like illness (ILI) were associated with cardiovascular disease mortality in older patients [11]. A cross-sectional study of over 80,000 adults hospitalized with confirmed influenza found that 12% had an acute cardiovascular event [12]. The economic burden on healthcare systems and societies as a result of influenza-associated hospitalizations can therefore be significant [13–15].

In Australia, recorded rates of death per 100,000 persons due to influenza in 2017 were 1.0, 4.5, 6.7 and 14.8 in those aged 45–64, 65–69, 70–74, and 75–79 years, respectively, with substantial further increases as age increased [16]. Three Australian modelling studies showed an estimated annual average of 6,700–8,900 respiratory hospitalisations attributable to influenza in adults 65 years and over [17–19].

Older adults are eligible for free influenza vaccination in Australia under National Immunisation Programme (NIP). Australia had a severe influenza season in 2017, and it was reported that 91% of influenza-related deaths were in adults aged 65 years and over [20]. The dominant strain circulating during the 2017 season was A/H3N2, and a low vaccine effectiveness of 10% was observed for this subtype [21]. Then, two enhanced influenza vaccines were introduced in Australia in 2018 for adults aged ≥65 years (hereafter referred to as 'older adults') under the NIP: high-dose trivalent unadjuvanted vaccine (HD-TIV; also known as HD-IIV3; Fluzone® High-Dose, Sanofi Pasteur) and standard dose trivalent MF59-adjuvanted vaccine (aTIV; also known as aIIV3; Fluad®, Seqirus) [22]. However, in 2019 only aTIV was funded for older people by the NIP.

At the time, there were no studies directly comparing HD-TIV with aTIV, and their effectiveness in the older Australian population was not clear. Although both vaccines have been shown to be effective in older adults [23–25], independent reviews by the Canadian National Advisory Committee on Immunization (NACI) [26,27] and European Centre for Disease Control and Prevention (ECDC) [28], both gave a higher grading of evidence in support of the use of HD-IIV3. The Canadian NACI has rated the evidence for the superiority of HD-TIV vs SD-TIV in older adults as Grade A (i.e. of high quality), and the evidence for the efficacy of aTIV in elderly adults as Grade B (i.e. of moderate quality) [26,27]. The benefits of HD-TIV, containing 60 μg HA per strain versus unadjuvanted standard-dose vaccine containing 15 μg HA per strain (SD-TIV; also known as SD-IIV3; Fluzone, Sanofi Pasteur), in adults aged ≥65 years have been extensively documented through a large randomised controlled study of efficacy [29,30], observational studies [31,32], and a meta-analysis [23].

A recent retrospective cohort study in older patients reported that the relative vaccine effectiveness of HD-TIV versus aTIV was 12% (95% confidence interval [CI]: 3.3–20%) for respiratory-related hospitalizations and 7% (95% CI: 2.3–12%) for cardiorespiratory hospitalizations during two influenza seasons (2016/17 and 2017/18) in the US [32].

Due to the co-circulation of any of two influenza A strains and two B lineages, the World Health Organization (WHO) also recommends the use of quadrivalent influenza vaccines (QIV). QIV demonstrated similar efficacy to the trivalent vaccine strains and had high immune response to the additional B lineage not included in the TIV [33]. It has been documented through an immunobridging study that the rVE of HD-QIV versus SD-QIV is equivalent to HD-TIV versus SD-TIV [34]. Given this equivalence, although based on epidemiological in which trivalent vaccines were used, the results are applicable to the current recommended quadrivalent vaccines. The objective of our modelling study was to estimate the incremental health and economic impact of using HD-TIV instead of aTIV under the NIP on respiratory and circulatory hospitalizations of older people (those aged ≥65 years) in Australia.

2. Methods

2.1. Study design, population and data sources

This is a modelling study comparing predicted hospitalization outcomes between people receiving HD-TIV and aTIV during an average influenza season. The study used hospitalization records of Australian adults ≥65 years of age from the National Hospital Morbidity Database from the Australian Institute of Health and Welfare [AIHW], Australian Government. In order to compute the average season hospitalization data (from 01 April to 30 November) were obtained from AIHW during 15 influenza seasons (2002–2017, excluding the 2009 H1N1 [human swine] influenza pandemic) [35].

Admissions with a principal diagnosis according to the ICD–10 AM (International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification) of respiratory (J00 to J99) and circulatory (I00-I99) diagnoses were included. The model accounted for the incidence rates of respiratory and circulatory plus respiratory hospitalizations.

2.2. Outcomes

The primary outcome was hospitalization for respiratory disease. A secondary outcome was hospitalization for circulatory plus respiratory disease.

2.3. Modelling

The model estimates respiratory, and circulatory plus respiratory hospitalizations that could be prevented if HD-TIV was used instead of aTIV. The hospitalization rate comes from a population with a mix of unvaccinated, SD-TIV, aTIV, and HD-TIV members:

$$\text{i)}\ R_{AUS} = F_{unvacc}R_{unvacc} + F_{SD}R_{SD} + F_{adj}R_{adj} + F_{HD}R_{HD}$$

where R_X stands for the hospitalization rates for the vaccine X.

As there is no direct measure for these outcomes, we used an indirect calculation to perform this estimation, using data on the relative vaccine efficacy/effectiveness (rVE) of HD-TIV versus both SD-TIV [29,30] and aTIV [32] for the health outcomes considered:

$$\text{ii)}\ R_{SD} = RR_{unvacc\to SD}\cdot R_{unvacc} \quad \text{where} \quad RR_{unvacc\to SD} = 1 - VE_{SD}$$

$$iii)\ R_{HD} = RR_{SD\to HD}\cdot R_{SD} \quad \text{where} \quad RR_{SD\to HD} = 1 - rVE_{SD\to HD}$$

$$iv)\ R_{HD} = RR_{adj\to HD}\cdot R_{adj} \quad \text{where} \quad RR_{adj\to HD} = 1 - rVE_{adj\to HD}$$

Solving the equations i) - iv) for R_{adj} we obtain:

$$R_{adj} = R_{AUS}\cdot\left(\frac{F_{unvacc}RR_{adj\to HD}}{RR_{SD\to HD}RR_{unvacc\to SD}} + \frac{F_{SD}RR_{adj\to HD}}{RR_{SD\to HD}} + F_{adj} + F_{HD}RR_{adj\to HD}\right)^{-1}$$

This equation holds for both respiratory, and circulatory plus respiratory hospitalizations, so it has been duplicated (with their respective R_X,$RR_{X\to Y}$, etc) in order to estimate the avoided hospitalizations for each outcome. $rVE_{SD\to HD}$ was obtained from the HD-TIV phase IV randomized clinical trial in which HD-TIV showed a relative vaccine efficacy of 27.4% against respiratory hospitalization and 17.7% against circulatory plus respiratory or cardiorespiratory hospitalization compared to SD-

TIV [29,30]. $rVE_{adj \rightarrow HD}$ was sourced from a retrospective cohort study in which rVE of HD-TIV versus aTIV was 12% for respiratory-related hospitalizations and 7% for cardiorespiratory ones [32,36]. Finally, to our knowledge, there is no data on the absolute vaccine effectiveness of SD-TIV (VE_{SD}) for these outcomes on the older adult population; we considered a range of potential values of VE of SD-TIV (20–70%) in the study.

For both, respiratory, and circulatory plus respiratory outcomes, the starting point is the number of reported hospitalizations, averaged over 15 seasons between 2002 and 2017 excluding 2009. In this period the target group was vaccinated with SD-TIV, with a vaccination coverage rate of 75% [37]. For each value of the VE of SD-TIV, we estimated the number of hospitalizations that would have occurred in that period if HD-TIV were used instead of SD-TIV, using the reported rVE of 17.7% for cardiorespiratory [29] and 27.4% for respiratory illness [30]. Next, we estimated the number of hospitalizations that would have occurred in that period if aTIV was used, using the reported rVE for HD-TIV vs aTIV, 7% and 12% for cardiorespiratory and respiratory illness, respectively [32]. Finally, we estimated the number of hospitalizations that would be averted by using HD-TIV instead of aTIV.

Economic assessment of cost-benefit was based on the average unit cost per respiratory or circulatory event (Table 1), extracted from National Hospital Cost Database for the financial year 2019–2020. Hospitalisation costs due to respiratory and circulatory causes have been estimated using the National Hospital Cost Data Collection Public Hospitals Report, Round 24. The cost per episode of hospitalisation was based on the average cost, weighted by number of separations, of the Australian Refined Diagnosis-Related Groups (AR-DRG) codes E62A and E62B for respiratory causes and F41AB/F42AB/F60AB/F62ABC/F66AB/F72AB/B70ABCD for circulatory causes [38]. As the vaccine costs were confidential, we explored the range of price increments that could be justified by the savings in the model.

The 2018 population estimate was applied in the model to reflect a similar time period with hospital admission data in the study [39]. The estimated national influenza vaccine coverage for older adults was also included in the model [40,41]. The analysis was conducted based on key parameters that were influential in the model. The decision tree model was developed using Microsoft Excel®. As this was a modelling study based on de-identified, aggregated data, no ethical approval was required.

Table 1
Key decision tree model inputs.

Parameter	Estimate		Source/notes
Population of older Australians (≥65 years old)	3.91 million		Australian Bureau of Statistics [39]
Influenza vaccine uptake in older Australia during the study period	75%		2009 Adult Vaccination Survey, 2014 Newspoll Omnibus Survey on adult flu vaccinations [40,41]
A unit cost of ICD-coded respiratory hospitalization	AU$7,175		Australian Refined Diagnosis-Related Groups [51]; National Hospital Cost Data Collection, Public Hospitals Cost Report [38]
An average rate of ICD coded respiratory hospitalization in older Australians along influenza season	3,445 per 100,000 population-seasons		Hospital data from 2002 to 2017, excluding 2009 (H1N1 pandemic season). It was considered conservative given the increased laboratory testing in recent years [35]
A unit cost of ICD-coded circulatory disease	AU$ 7,829		Australian Refined Diagnosis-Related Groups; National Hospital Cost Data Collection, Public Hospitals Cost Report [38]
An average rate of ICD coded circulatory plus respiratory hospitalization in older Australians	10,393 per 100,000 population-seasons		Hospital data from 2002 to 2017, excluding 2009 (H1N1 pandemic season) [35]
Absolute effectiveness of SD-TIV against ICD-coded respiratory hospitalization	15% to 40%		Based on a series of publications, experts' advice and assumptions
Relative vaccine effectiveness against ICD-coded respiratory hospitalization	HD-TIV vs SD-TIV	27.4%	Based on correspondence with the authors of [Diaz Granados, 2014] [30]
	HD-TIV vs aTIV	12.0%	[van Aalst 2020] [32]
Relative vaccine effectiveness against ICD-coded circulatory plus respiratory hospitalization	HD-TIV vs SD-TIV	17.7%	[DiazGranados 2015] [29]
	HD-TIV vs aTIV	7.0%	[van Aalst 2020] [32]

ICD (International Statistical Classification of Diseases and Related Health Problems); aTIV, (MF59) adjuvanted trivalent influenza vaccine; HD-TIV, high-dose trivalent vaccine;
SD-TIV, standard dose trivalent influenza vaccine.

3. Results

Between 2002 and 2017, the average respiratory hospitalization rate among older people during influenza season (April-November) was 3,445/100,000 population-seasons (Table 1), with an average cost of AU $ 7,175 per admission.

Similarly, the average circulatory plus respiratory hospitalization rate among older Australians during influenza season (2002–2017) was 10,393/100,000 population-seasons, with an average cost of AU$ 7,829 per admission. Hospitalizations and hospitalization rate by year are shown in Table 2.

Tables 3 and 4 show the modelled results for a range (20%–70%) of assumed VE values of SD-TIV versus no vaccination on the relevant outcomes. For each assumed VE, VE values for aTIV versus no vaccination and HD-TIV versus no vaccination are presented. From these, the hospitalization rate per 100,000 population and the resultant number of hospitalizations could be estimated. The final columns of the Tables show the estimated number of hospitalizations that could have been averted if HD-TIV had been used instead of aTIV in older Australians in 2019, and the resultant cost savings, based on a cost of $7,175 per hospitalization.

It was estimated that a publicly funded vaccination program using HD-TIV instead of aTIV for older Australians, may avert an additional 6,315–9,410 respiratory admissions each year, with an incremental healthcare cost saving of AU$ 15.9–38.2 million per year (Table 3). A publicly funded vaccination program using HD-TIV instead of aTIV for older adults, may avert 11,921–17,765 circulatory plus respiratory admissions (Table 4), resulting in healthcare cost savings of AU$ 64.0–109.8 million per year (Table 4).

As shown in Table 5 when considering the base case with SD-TIV, VE = 50%, the savings accrued by averted circulatory plus respiratory or cardiorespiratory events would justify a price increment of HD-TIV versus aTIV of AU$ 40.32 (even with variation in the price of aTIV).

Fig. 1 (a and b) shows the scenario analysis for the different values of SD-TIV VE, from 20% to 70%, the lower VE of SD-TIV, the higher the savings (due to rVE definition). HD-TIV savings, generated by a full switch from aTIV to HD-TIV, decrease with increasing SD-TIV VE. Increasing SD-TIV VE reduces the impact of the relative vaccine efficacy parameters, which is evident as a reduced difference in absolute efficacy between the two vaccines being compared (aTIV and HD-TIV). A reduced difference in the efficacies of aTIV and HD-TIV VE leads to a reduced number of avoided hospitalizations and hence, a decrease in avoided costs/savings. Similarly, with lower SD-TIV VE, the difference in VE of HD-TIV and aTIV is significant and thus, avoided clinical outcomes and savings are higher.

Table 2
Respiratory and circulatory plus respiratory hospitalization rates for older Australians per influenza season (April-November), 2002–2017.

Calendar year	Number of hospitalisations in Australians aged 65 + years		65 + Population (N)	Incidence (per 10^5) respiratory	Incidence (per 10^5) circulatory plus respiratory
	Respiratory admissions ICD-10 codes, J00-J99	Circulatory admissions ICD-10 codes, I00-I99			
2002	86,229	182,746	2,465,669	3,497	10,909
2003	85,200	183,244	2,511,327	3,393	10,689
2004	83,644	184,477	2,558,857	3,269	10,478
2005	84,351	185,849	2,611,879	3,230	10,345
2006	83,663	189,863	2,664,064	3,140	10,267
2007	89,702	189,091	2,736,610	3,278	10,188
2008	95,802	196,115	2,805,167	3,415	10,406
2010	95,867	206,358	2,986,675	3,210	10,119
2011	101,937	214,611	3,087,911	3,301	10,251
2012	111,810	211,830	3,213,853	3,479	10,070
2013	105,254	215,694	3,330,378	3,160	9,637
2014	119,029	218,773	3,442,148	3,458	9,814
2015	132,207	240,668	3,554,304	3,720	10,491
2016	142,704	258,687	3,672,251	3,886	10,930
2017	160,561	267,927	3,790,842	4,235	11,303
Average values 2002–2017				**3,445**	**10,393**

Data for each calendar year were obtained from AIHW. The peak of influenza circulation in Australia is considered from April to November.
Data for 2009 were excluded due to the H1N1pdm09 (human swine) influenza pandemic.

Table 3
Estimated respiratory hospitalization rates and associated cost savings in different scenarios of assumed aTIV effectiveness.

Assumed VE of SD-TIV VE vs no vaccination on respiratory hospitalizations	VE of aTIV vs no vaccination	VE of HD-TIV vs no vaccination	Modelled situation: aTIV used for older Australians		Modelled situation: HD-TIV used for older Australians		Averted hospitalizations: number	Associated savings if vaccination is switched to HD-TIV
			Hospitalization rate per 10^5 inhabitants	Hospitalization number	Hospitalization rate per 10^5 inhabitants	Hospitalization number		
20%	34.0%	41.9%	2,675	78,417	2,354	69,007	9,410	$38,199,482
30%	42.3%	49.2%	2,567	75,255	2,259	66,225	9,031	$35,477,018
40%	50.5%	56.4%	2,436	71,416	2,144	62,846	8,570	$32,171,168
50%	58.8%	63.7%	2,274	66,655	2,001	58,656	7,999	$28,071,915
60%	67.0%	71.0%	2,067	60,595	1,819	53,324	7,271	$22,854,683
70%	75.3%	78.2%	1,795	52,622	1,580	46,307	6,315	$15,989,904

VE, vaccine effectiveness; vs, versus; SD-TIV, standard dose trivalent vaccine; aTIV, adjuvanted trivalent vaccine; HD-TIV, high dose trivalent vaccine.

Table 4
Estimated circulatory plus respiratory hospitalization rates and associated cost savings in different scenarios of assumed aTIV effectiveness.

Assumed VE of SD-TIV VE vs no vaccination on circulatory plus respiratory hospitalizations	VE of aTIV vs no vaccination	VE of HD vs no vaccination	Modelled situation: aTIV used for older Australians		Modelled situation: HD-TIV used for older Australians		Averted hospitalizations: number	Associated savings if vaccination is switched to HD-TIV
			Hospitalization rate per 10^5 inhabitants	Hospitalization number	Hospitalization rate per 10^5 inhabitants	Hospitalization number		
SD-TIV VE against circulatory plus respiratory hospitalizations	VE aTIV(vs no vaccination)	VE HD(vs no vaccination)	aTIV		HD-TIV		Averted circulatory plus respiratory hospitalizations	HD switch savings
			Hospitalization rate per 10^5 inhabitants	Hospitalization number	Hospitalization rate per 10^5 inhabitants	Hospitalization number		
20%	29.2%	34.2%	8656	253,785	8051	236,020	17,765	$109,764,305
30%	38.1%	42.4%	8307	243,552	7726	226,503	17,049	$104,156,162
40%	46.9%	50.6%	7884	231,126	7332	214,947	16,179	$97,346,275
50%	55.8%	58.9%	7358	215,717	6843	200,617	15,100	$88,902,014
60%	64.6%	67.1%	6689	196,107	6221	182,379	13,727	$78,154,773
70%	73.5%	75.3%	5809	170,303	5402	158,382	11,921	$64,013,667

VE, vaccine effectiveness; vs, versus; SD-TIV, standard dose trivalent vaccine; aTIV, adjuvanted trivalent vaccine; HD-TIV, high dose trivalent vaccine.

4. Discussion

Enhanced vaccines for older adults are a solution to the reduced protection provided by standard dose vaccines in this population. The higher effectiveness of these vaccines may extend to circulatory disease prevention compared with standard-dose influenza vaccines [42], and differences between the available enhanced vaccines may also be important. This study showed that using HD-TIV instead of aTIV for

Table 5
Vaccine effectiveness and related costs between high dose and adjuvanted TIV (at base case scenario for circulatory plus respiratory hospitalizations using the standard dose VE at 50%).

	aTIV	HD	rVE (HD vs aTIV)
Absolute VE	55.8%	58.9%	7.0%
Outcomes	**aTIV**	**HD**	**Difference**
Hospitalization rate (/10^5)	7,357.9	6,842.9	515.0
Hospital admissions	215,717	200,617	**15,100**
Costs (per person)	**aTIV**	**HD**	**Difference**
Hospitalization cost	$576.05	$535.73	$40.32
Vaccination cost	$40.00	$80.32	−$40.32
Total cost	$616.05	$616.05	$0.00

VE, vaccine effectiveness; aTIV, adjuvanted trivalent vaccine; HD, high dose trivalent vaccine; rVE, relative vaccine efficacy/effectiveness.

older Australians could lead to incremental health and economic gains, due to further reductions in respiratory and circulatory hospitalizations.

In the 2019 influenza season, a severe H3N2 season, 313,033 cases of laboratory-confirmed influenza infections were notified to the National Notifiable Diseases Surveillance System, with 953 deaths, which was higher than the previous five year average (n = 404) in Australia [43]. The median age of people who died was 86 years of age, highlighting the increased risk of influenza-related morbidity and mortality in this age group [43], and the need for more immunogenic vaccines for older adults.

A review by the Canadian National Advisory Committee on Immunization (NACI) concluded that there is strong evidence that HD-TIV provides superior protection compared with SD-TIV in the elderly [27]. A separate 2019 review on high-dose influenza vaccination indicated that in elderly adults aged ≥ 65 years, HD-TIV had comparable or greater effectiveness at reducing influenza illness, hospitalization, and mortality, compared with SD-TIV and SD-QIV [42]. HD-TIV also appeared to be more cost-effective from a United States and Canadian perspective than SD-TIV, no vaccination, and standard dose quadrivalent vaccination [42]. A recent modelling study suggested that HD-TIV is associated with reduced hospitalization costs compared with aTIV in older patients in the US [44]. Another study conducted in England and Wales reported the beneficial impact of vaccination with HD-TIV compared to aTIV in the study, with 13,092 fewer lab-confirmed influenza cases, 1,109 fewer influenza-related deaths, 4,637 less influenza/

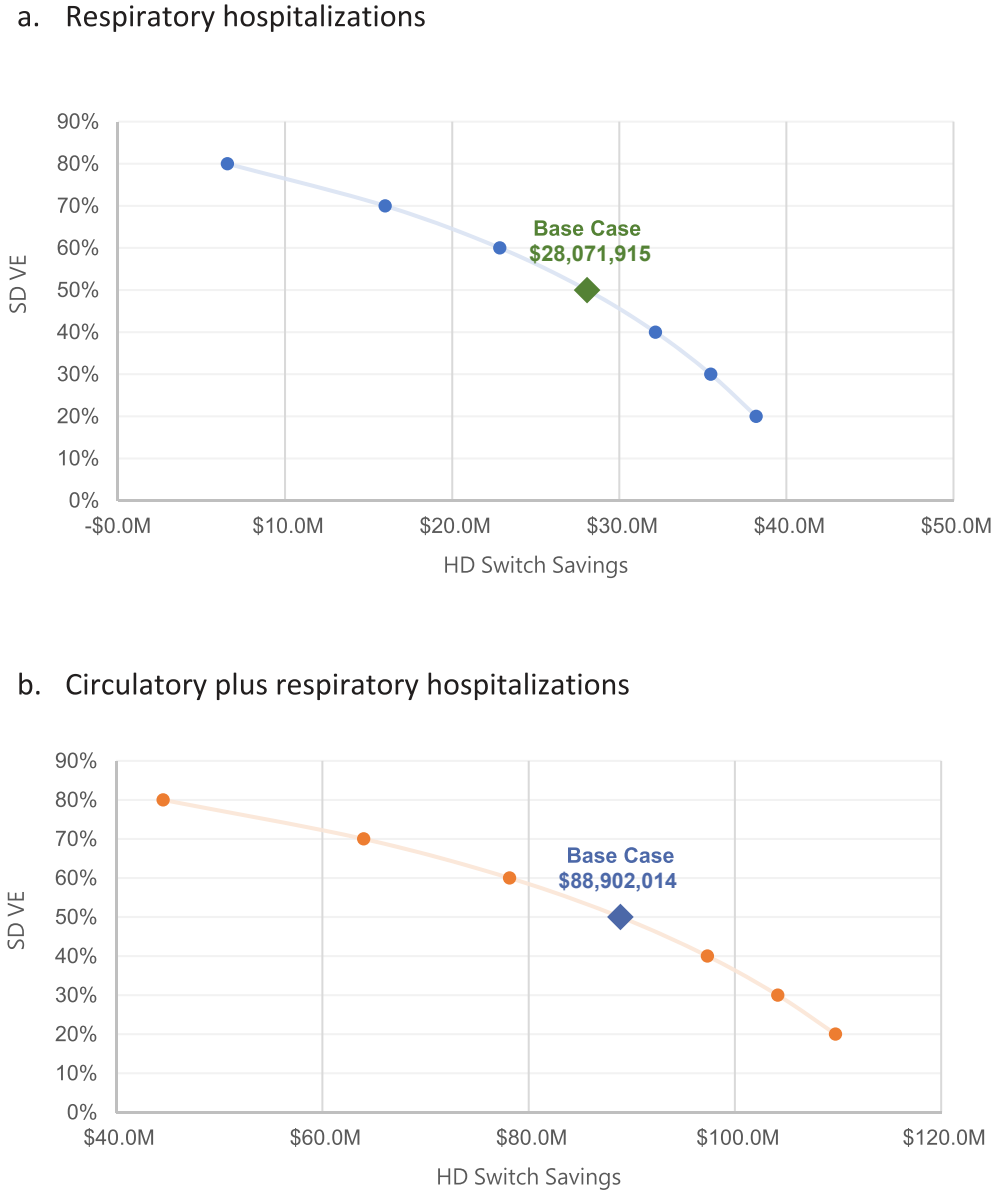

Fig. 1. Scenario analyses of SD-TIV vaccine effectiveness and cost savings (a full switch from aTIV to HD-TIV).

pneumonia hospitalizations and 3,245 fewer GP consultations among adults aged 65 years and over [45]. In addition, authors also stated that 21,128 respiratory hospitalizations would be avoided per influenza season if HD-TIV was used in this population rather than aTIV. The incremental cost effectiveness ratio for HD-TIV versus aTIV per quality-adjusted live years was £2,800, with incremental population costs were £ 13.7 million for respiratory hospitalizations in the study [45]. Further research is needed to determine whether high-dose quadrivalent influenza vaccines will provide superior protection compared to MF59-adjuvanted quadrivalent influenza vaccine.

Cardiovascular disease is the leading cause of morbidity and mortality in the world, and there is ample evidence of the relationship between influenza infection and cardiovascular events [46,47]. Studies including a randomised clinical trial, have shown the considerable evidence that influenza vaccination may prevent cardiovascular related events in adults and older people [36,48]. Reduction in burden of influenza-associated illness including influenza-attributable cardiovascular events by the vaccine is significant and a highly cost-effective public health intervention. Any incremental reduction in cardiovascular disease events by influenza vaccination will have a considerable public health impact.

This analysis builds on a previous modelling study comparing hospitalization costs when using HD-TIV versus aTIV. That study only included VE estimates from two influenza seasons, both of which were dominated by influenza A/H3N2 [44]. In contrast, our study is valuable because the data covers 15 influenza seasons' of hospitalization records, which takes into account the seasonal variation of influenza epidemiology in Australia. This is important, since the severity, dominant influenza strain, and influenza vaccine effectiveness vary from year to year [49].

This analysis of the benefit of HD-TIV versus aTIV was based on a US study directly comparing them in real-world settings, which had several key strengths [32]. Firstly, the study adjusted for confounders using the previous event rate ratio (PERR) method for unmeasured variables and regression for measured variables. Second, it included a negative control outcome of urinary tract infection admissions where an association between vaccination status and clinical outcome could not be identified. Finally, it included extensive testing and confirmation of assumption validity with various sensitivity analyses.

Our study has important limitations that should be considered when interpreting our findings. First, the findings from the vaccine effectiveness study in the United States may not be directly translatable to the Australian settings. Second, the original study in the United States was conducted in two A/H3N2 dominant seasons, which means it might not be possible to fully generalize and apply these results to years/seasons that were dominated by A/H1N1 and influenza B strains. However, most severe influenza cases in older Australians are due to influenza A/H3N2 virus [50]. Third, at the time of this study, there was no data on the relative vaccine effectiveness of HD-TIV versus aTIV on circulatory hospitalizations because of the low number of cardiovascular events compared to respiratory ones in the FIM12 trial [29]. For this reason, we used rVE for cardiorespiratory events as a proxy. Finally, these results are based on efficacy evidence related to trivalent influenza vaccines. Even if immunobridging studies [34] support its applicability to currently recommended quadrivalent influenza vaccines, some minor differences should be expected depending on the strain in the circulation and efficacy of the fourth vaccine strain.

In conclusion, our study found that using HD-TIV instead of aTIV for vaccination against seasonal influenza in older Australians may lead to significant health and economic savings due to the reduction in hospitalization for respiratory and circulatory complications attributable to influenza.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. JKY, CF, RIM, ET, FPA, SC and NL are employees of Sanofi, a company that manufactures and commercializes influenza vaccines. C Raina MacIntyre receives funding from Sanofi for investigator-driven research on influenza epidemiology. She is on the WHO COVID-19 Vaccine Composition Technical Advisory Group and WHO Smallpox and Monkeypox Working Group, and received funding from the National Health and Medical Research Council and Medical Research Futures Fund.

Data availability

The authors do not have permission to share data.

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