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Modelling of optimal timing for influenza vaccination as a function of intraseasonal waning of immunity and vaccine coverage

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ABSTRACT

The influenza season in Australia usually peaks in August. Vaccination is recommended beginning in March-April. Recent studies suggest that vaccine effectiveness may wane over a given influenza season, leading to reduced effectiveness at the peak of the season. We aimed to quantify how changes in timing of influenza vaccination and declining vaccine coverage could change the percentages of prevented cases.

Results from a systematic review were used to inform calculation of a waning function over time from vaccination. Age specific notification data and vaccine effectiveness and coverage estimates from 2007 to 2016 (2009 influenza pandemic year excluded) were used to model a new notification series where vaccine effectiveness is shifted in time to account for delayed vaccination by month from March to August. A sensitivity analysis was done on possible vaccine coverage changes and considering time gap between vaccine uptake and recommendation.

Delaying vaccination from March to end of May prevents more cases over a season, but the variation in cases prevented by month of vaccination is not large. If delaying vaccination results in missed or forgotten vaccination and decrease coverage, delaying vaccination could have a net negative impact. Furthermore, considering a time gap between recommendation and uptake, earlier recommendation is more effective in preventing cases. The results are sensitive to assumptions of intra-seasonal waning of effectiveness. More research is required on intra-seasonal vaccine effectiveness waning and the effect of delayed vaccination on overall uptake to inform any potential changes to current vaccine scheduling recommendations.

1. Background

Seasonal influenza results in significant morbidity and mortality worldwide [1]. On average, there are more than 18,000 influenza-attributable hospitalisations annually in Australia, with the highest disease burden among the elderly and young children [2–8]. The influenza season occurs in the southern hemisphere in winter and usually peaks in August [2,9,10].

Influenza vaccines are the most effective means of preventing influenza [11]. Two factors are crucial for prevention: vaccine effectiveness (VE) and vaccination coverage (VC) [12]. High VC can induce herd immunity, an additional protection provided to unvaccinated individuals in a population as the result of disease transmission being interrupted by the vaccinated fraction of the population [13].

In Australia it is recommended to receive the annual influenza vaccination as soon the vaccine becomes available, typically in early autumn (March-April). Currently national recommendations are for all people over 6 months of age, with vaccine available free to high risk groups such as those aged 65 and over, under the National Immunisation Program [14,15]. However, influenza vaccine uptake is sub-optimal [16] and vaccine effectiveness is generally moderate and variable [17–23].

There is a growing body of evidence suggesting that influenza vaccine effectiveness may decrease significantly within a single influenza season [17,24–30]. The magnitude of this phenomenon may depend on which influenza virus type predominates in a given season [24,25,29,31]. A systematic review of test-negative studies evaluating the change in vaccine effectiveness over time within a single influenza season, which included a meta-analysis of vaccine effectiveness at 15–90 days post-vaccination compared to 91–180 days post-vaccination, showed a statistically significant

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decline in vaccine effectiveness for influenza A/H3 (33%) and influenza B (19%), but not influenza A/H1 (8%, non-significant) [31]. Waning vaccine effectiveness may also be more pronounced in the elderly due to immunosenescence [24,25,32]. The evidence of waning vaccine protection has been mixed, as some studies have observed only slight decreases in vaccine effectiveness within a single influenza season [33,34]. For instance, a test-negative study in the US observed no significant difference in vaccine effectiveness between 15 and 90 days post-vaccination and 91–180 days post-vaccination [34].

While several studies have explored vaccine effectiveness, little research has been done to determine the optimal timing of influenza vaccine administration, accounting for intraseasonal waning. One surveillance study across four influenza seasons in Spain attempted to determine whether late season vaccination, compared to early season vaccination, resulted in decreased odds of hospital admission for influenza. This showed that late vaccinators had lower odds of hospital admission, but only when influenza A (H3N2) is the predominant strain [24]. The effect of changing vaccine timing on both intra-seasonal waning and vaccine uptake at population level, on prevention of influenza has not yet been fully investigated.

In this study we aimed to model the effectiveness of vaccination by assuming vaccination being effective from each month in the six months range from March to August for an average Australian influenza season, using assumptions of intra-seasonal waning. We also aimed to determine the effect of reduced VC associated with delayed vaccination uptake and explored results on delaying recommendation when considering a time gap between vaccine recommendation and uptake [35,36].

2. Methods

2.1. Data

Data used were from 2007 to 2016, with 2009 excluded because this was a pandemic year. We used monthly age-specific laboratory confirmed notifications ($Ny(t)$) available from the Australian website NNDSS [37] for two age groups, <65 and 65+. For each year we used estimation of vaccine effectiveness in Australia adjusted for circulating strains and recipient age (VEy) [23,38,39]. We used vaccine coverage in Australia for each year as estimated in [16], (VCy) specific for age groups <65 and 65+ years old. Estimates were available for each year for the 65+ age group, however for the <65 age group, coverage was estimated until 2012 and where not available, we assumed it to be the same as for 2012 (this apply to 2013–2016). We applied this assumption based on a literature suggesting on average in Australia the coverage for each year in that age group is around 30% [40], in addition, coverage in >65 s has stayed quite constant in that time. Averaged over the nine influenza seasons, the coverage is 32% and 73% for <65 and 65+ respectively, and these values were used in the study. Finally, for vaccine effectiveness waning percentage over time from vaccination, we used results from a systematic review [31], which found a waning of 33% for A(H3N2), 19% for B and 8% for A(H1N1). Waning was found at 4–6 months following vaccination, but not in the first three months. We used 0% waning for A(H1N1) as no statistically significant waning was found. To consider a monthly delayed coverage from recommendation we used monthly uptake data from US [41] as Australian one was not available.

2.2. Model

To obtain a monthly waning function for each year ($Wy(t)$), firstly we calculated the weighted average for each strain, using 33% for A(H3N2), 19% for B and 0% for A(H1N1). Results of the annual weighted average between strains is showed in Table 1. The 2007 was a severe A(H3N2) season, for which we did not have data for the proportion of each strain, so for this year we assumed the same waning as in another severe A(H3N2) season, 2012. The systematic review [31] showed waning effectiveness after 4–6 months following vaccination, therefore, we attributed the waning percentage found to the middle point of the interval (at 5 months following vaccination). We had the value of the waning function, $Wy(t)$, for month t = 1 ($Wy(1) = 0\%$ maximum effectiveness in the first month following vaccination) and t = 5 (last column of table 1) following vaccination for each year. We used a linear decline over months from vaccination and obtained the waning function by month for each year $Wy(t)$, with y = 2007,2008,2010 to 2016 and t = 1,. . .,12.

To get a time dependent vaccine effectiveness (VEy(t), where t is months from vaccination), from the available yearly estimates (VEy), we applied the waning functions to each yearly effectiveness as follows:

$$VEy(t) = VEy * (1 - Wy(t)) \text{ with } y = 2007, 2008, 2010 \text{ to } 2016 \text{ and } t = 1, \cdots, 12 \quad (1)$$

We then used vaccine coverage and effectiveness to get the proportion of prevented cases from vaccination for each year as

$$Py(Tr) = VCy(Tr) * VEy(t) \quad (2)$$

where Tr is the month of vaccination recommendation. To obtain a new incidence series (notification data) $N'y(t)$ from the available notification data $Ny(t)$, to have comparator epidemic data without any vaccination effect (baseline scenario), we used the estimates proportion of prevented cases from vaccination to remove the vaccination effect as:

$$N'y(t) = Ny(t)/(1 - Py(Tr)) \text{ with } y = 2007, 2008, 2010 \text{ to } 2016 \text{ and } t = 1, \cdots, 12 \quad (3)$$

Due to the luck of Australian estimates for coverage by month, to compute the new notification series, we assumed in the base case scenario that people would get vaccinated by April, which is the standard timing for Australia's vaccine recommendation. However, a different coverage assumption is explored in the sensitivity analysis.

Finally, we used this base case scenario without vaccination effect to add the effect of vaccination for the 6 different vaccination scenarios (where the vaccine induce immunity is achieved in March, April, May, June, July or August) as follows

$$N''y(t) = N'y(t) * (1 - Py(Tr')) \quad (4)$$

where the vaccine effectiveness is adjusted for a monthly shift in time (t') for each month from March to August as

$$Py(Tr) = VCy(Tr) * VEy(t') \quad (5)$$

where t' = t + δ and δ depends from the number of months we delay the vaccine uptake

We show results for 6 different vaccination scenarios: vaccination induced immunity being achieved in March, April, May, June, July or August; and results are shown as the number of prevented notified cases. Results are shown as time to achieve vaccine effectiveness, given that seroconversion and immunity occurs on average 2–3 weeks after vaccination, depending on recipient age.

2.3. Sensitivity analysis

We conducted a sensitivity analysis on monthly waning percentage of vaccination effectiveness and decreasing coverage, to test the possible trade-off between reduced waning and reduced

Table 1
Percentage of waning vaccine effectiveness between first month and 5th month following vaccination, weighted for each year between the proportion of each circulating strain (table shows number of cases and proportion for each strain and year).

Year	A(H1N1) (0%)	A(H3N2) (33%)	B (19%)	weighted waning (%_y)
2007				28.67%
2008	1329 (15%)	2578(29%)	4899 (56%)	20.23%
2010	11,173 (84%)	815 (6%)	1304 (10%)	3.89%
2011	15,246 (57%)	4305 (16%)	7249 (27%)	10.44%
2012	1334 (3%)	32,041 (73%)	10,394 (24%)	28.67%
2013	12,322 (45%)	5038 (18%)	10,200 (37%)	13.06%
2014	32,140 (48%)	26,255 (40%)	7940 (12%)	15.36%
2015	10,135 (10%)	28,881 (29%)	60,212 (61%)	21.13%
2016	28,640 (32%)	50,904 (55%)	9594 (13%)	20.89%

vaccine coverage. To test the results sensitivity to monthly percentage of VE waning, we kept coverage constant in each scenario and halved the waning. To test the results in the case of changing coverage, we decreased it by 5% and 2% monthly respectively for 65 + and <65, while delaying vaccination. Those two values were chosen based on the coverage value changing over years, due to the lack of estimates we chose reasonably possible values and did a sensitivity analysis to find the threshold values for coverage drop, that when crossed, resulted in a negative impact in delaying vaccination uptake. We compered the number of prevented cases in each scenario with the assumption of 75% and 30% coverage in March, 70% and 28% in April, and so on until 50% and 20% coverage in August, respectively for 65+ and <65 age group. Furthermore, previous results are showed for an ideal situation in which we assumed that the proportion of the population vaccinated every year gets the vaccination in a month window following recommendation. This assumption was made to show the net impact of vaccine waning effectiveness and decreasing vaccination coverage in an ideal situation. However, we did a sensitivity analysis to explore a more realistic scenario in order to include the delay between the recommendation timing of vaccination and the actual vaccination uptake timing. In this scenario, the estimated annual coverage in each age-group is reached at the end of the season, with a monthly distribution of new vaccinated cohorts coming in every month from the vaccine recommendation uptake. In absence of Australian monthly coverage data for influenza vaccination, we used US seasonal coverage distribution from September to August estimated in 2017–2018 season for the age groups 18–64 and 65+ (41), adapted to the Australian season from March to February (Table 2). In this scenario, we used the estimates of annual vaccine coverage by months Tr from vaccine recommendation ($VCy(Tr)$) and the obtained monthly vaccine effectiveness ($VEy(t)$), by time t from vaccination to obtain the proportion of prevented cases by vaccination in each months from the start of vaccine recommendation as:

$$Py(Tr) = \sum_{i=0}^{Tr-1} VCy(Tr-i) * VEy(i+1) \text{ with } i = 1 \cdots 11; \quad (2)$$

Where the yearly prevented cases can be expressed as the sum of monthly prevented cases as

$$Py = \sum\nolimits_{Tr=1}^{12} Py(Tr) \quad (2a)$$

Or can be expressed as the sum of each new monthly vaccinated cohort from the recommendation month as

$$Py = \sum\nolimits_{Tr=1}^{12} [VCy(Tr) * \sum\nolimits_{t=1}^{12-(Tr-1)} VEy(t)] \quad (2b)$$

We showed results for an averaged influenza notification series and vaccination effectiveness waning (averaged over the 9 years data).

Table 2
Percentages of monthly increasing cumulative coverage and incremental monthly coverage of the total proportion of the estimated vaccinated population for each year at the end of the season.

US monthly season from vaccine availability	Australian season adaptation from vaccine availability	<65 Cumulative (incremental) proportion of total coverage	65+ Cumulative (incremental) proportion of total coverage $VCy(Tr)$
September	March	19% (19%)	22.3% (22.3%)
October	April	56.3% (34.3%)	63.6% (41.3%)
November	May	75.6% (19.3%)	81.9% (18.3%)
December	June	83% (7.4%)	87.7% (5.8%)
January	July	90.1% (7.1%)	93.3% (5.6%)
February	August	95.9% (5.8%)	96% (2.7%)
March	September	97.7% (1.8%)	98% (2%)
April	October	99% (1.3%)	99% (1%)
May	November	100% (1%)	100% (1%)
June	December	100% (0%)	100% (0%)
July	January	100% (0%)	100% (0%)
August	February	100% (0%)	100% (0%)

3. Results

During the period between 2007 and 2016 (excluding the pandemic influenza season in 2009), the annual influenza season took place between July and October, with peaks around mid-August.

Defining the start season as the month in which the number of influenza notification contributed >5% of the total influenza cases for that season, there were only two early seasons (2011 and 2012) which started in the first month of winter (June), and two late season which peaked in the first month of spring (September), 2008 and 2010 (Fig. 1); however, the peak did not occur earlier than August in any year.

Vaccine effectiveness changes depending on vaccine match each year as well as vaccine waning depending on circulating strains (Fig. 2). Fig. 2 shows that 2007 had the fastest decline in time from vaccination due to A(H3N2) being the predominant strain. In years where the predominant strain was A(H1N1), such as 2010, 2014 or 2016, vaccine effectiveness declined less over time from vaccination.

Fig. 3 shows the average cases without any vaccination (blue line) and for all the other scenarios with vaccination delivered in each month from March to August. Fig. 4 shows the results as number of prevented cases for each vaccination timing scenario, with more cases prevented with later vaccination. As showed in Fig. 3, delaying vaccination will fail to prevent cases early in the season, however it will be more effective in preventing cases closer to the peak. The difference between cases without intervention (blue line in Fig. 3) and cases with vaccination by month of the season is listed in Table 2, while the total number of prevented cases for the entire season (TOT in the table) is shown by age-group in Fig. 4.

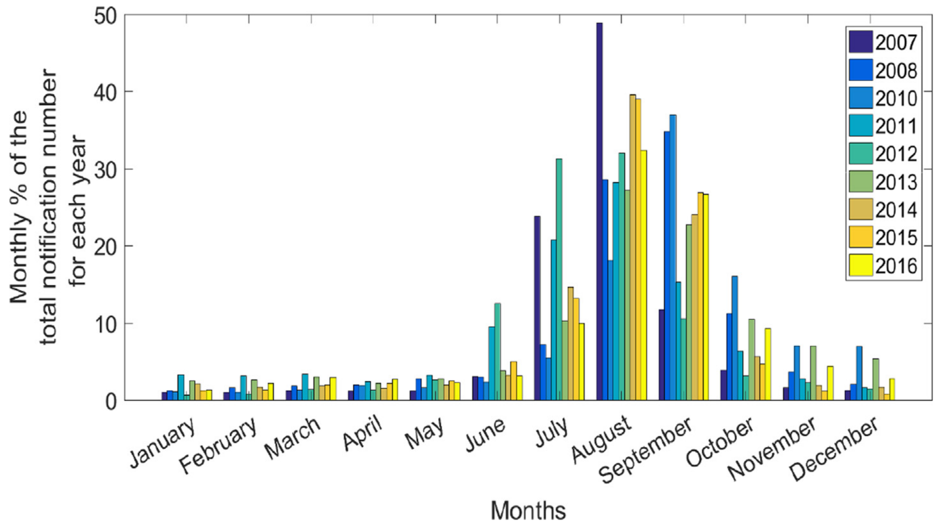

Fig. 1. Percentages of the annual total notification number by month for each year, NNDSS [35].

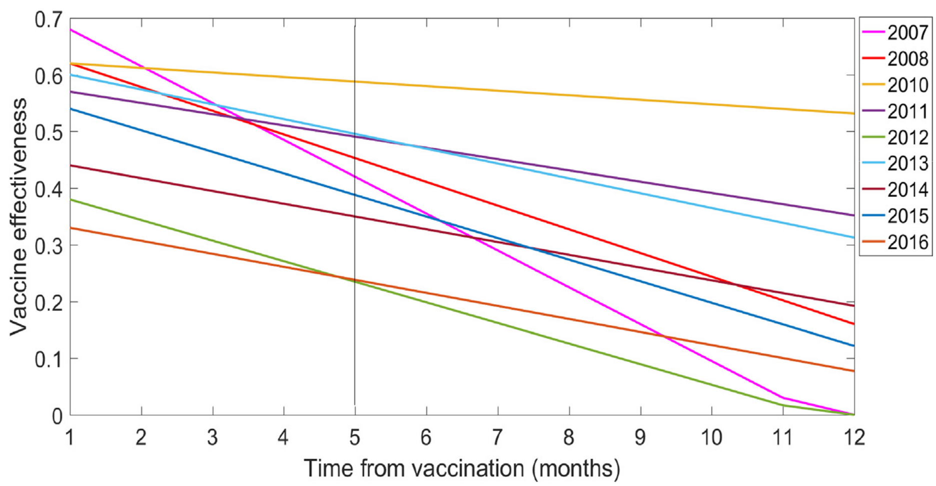

Fig. 2. Vaccine effectiveness waning over time from vaccination for each year from linear interpolation of the values at month 1 and 5.

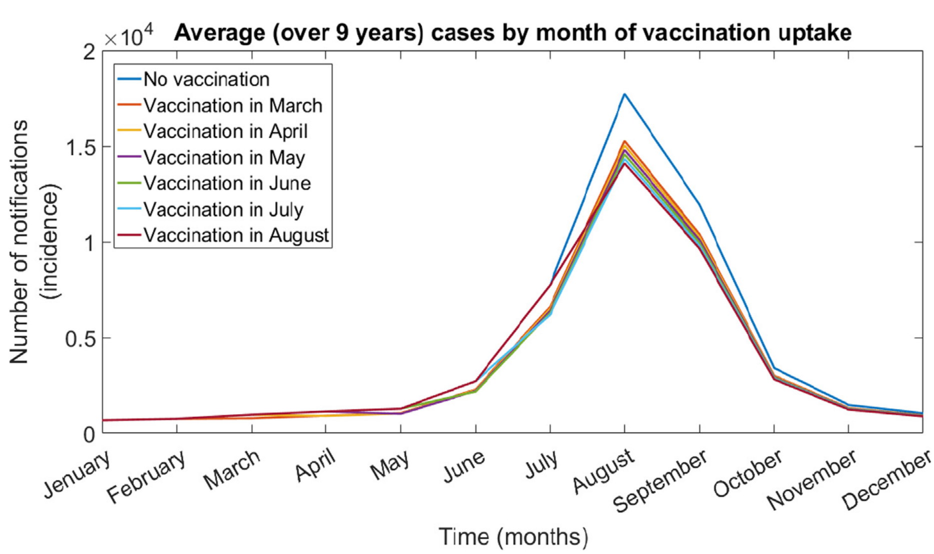

Fig. 3. Average notification of cases without any vaccination (blue line) and for all the other scenarios with vaccination effectiveness achieved in each month from March to August. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

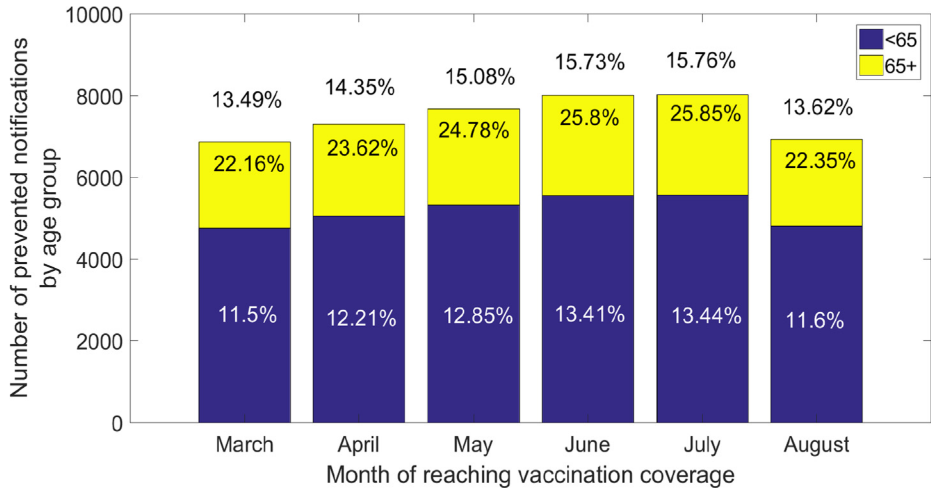

Fig. 4. Number and % of prevented cases by age group (<65 and 65 +) and total, by varying month of vaccination from March to August.

Due to higher coverage in the 65+, this age group has higher prevention of influenza. Table 3 shows number of cases prevented by month for each vaccination scenario for the total population. The highest number of cases prevented is if vaccination starts to be effective in June and July, which makes May/June the optimal month for vaccination, considering 2–3 weeks for vaccine response. Fig. 4 shows the number and percentage of prevented cases in each age group, and the total population.

3.1. Sensitivity analysis

Fig. 5 shows the prevented cases if delayed vaccination results in decreasing coverage. If coverage decreases 5% and 2% each month respectively for the age groups 65+ and <65 years, earlier vaccination is favoured. Furthermore, when considering a time gap between vaccination recommendation and uptake with the inclusion of a monthly incremental coverage from the recommended month, we found that earlier recommendation for vaccine uptake is more effective in preventing influenza cases (Fig. 6).

4. Discussion

Under assumptions of waning immunity, varying the time of vaccination affects the prevented fraction of influenza, but reasonable population protection is achieved at all time points. We found that delayed vaccination may be more optimal than early

Table 3
Prevented cases each month for an average Australian season within each vaccination scenarios, for total population.

Month of initial vaccine protection	Prevented cases by month from January to December for an average season for the total population (where average number of total cases without vaccination is 50899)												Total cases prevented
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	
March	0	0	189	219	231	432	1127	2459	1545	401	159	105	6867
April	0	0	0	233	248	468	1231	2694	1695	440	176	117	7302
May	0	0	0	0	264	505	1335	2929	1845	480	192	128	7678
June	0	0	0	0	0	541‘	1439	3164	1995	519	209	140	8006
July	0	0	0	0	0	0	1543	3399	2145	558	226	151	8021
August	0	0	0	0	0	0	0	3633	2295	597	242	162	6930

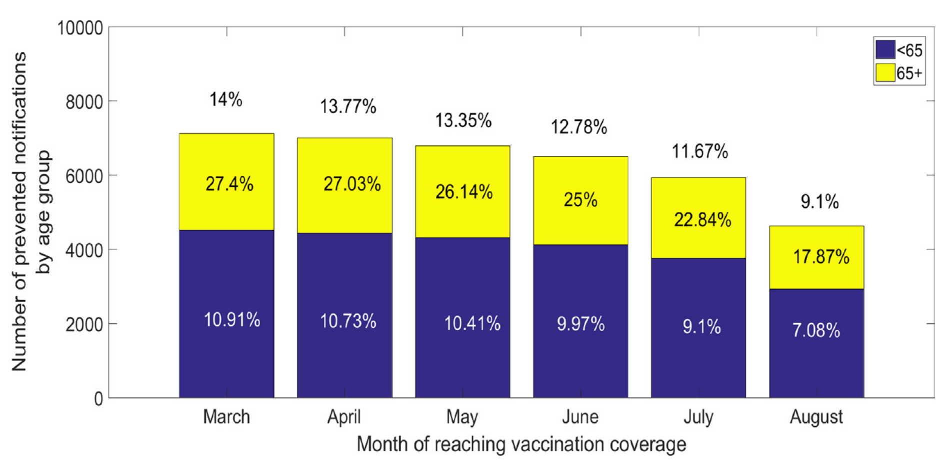

Fig. 5. Number and % of prevented cases by age group (<65 and 65 +) and total, by varying month of vaccination from March to August, with decreasing coverage by 5% and 2% each month starting in April with a baseline of 75% and 30% coverage respectively for 65 + and <65 age group in March.

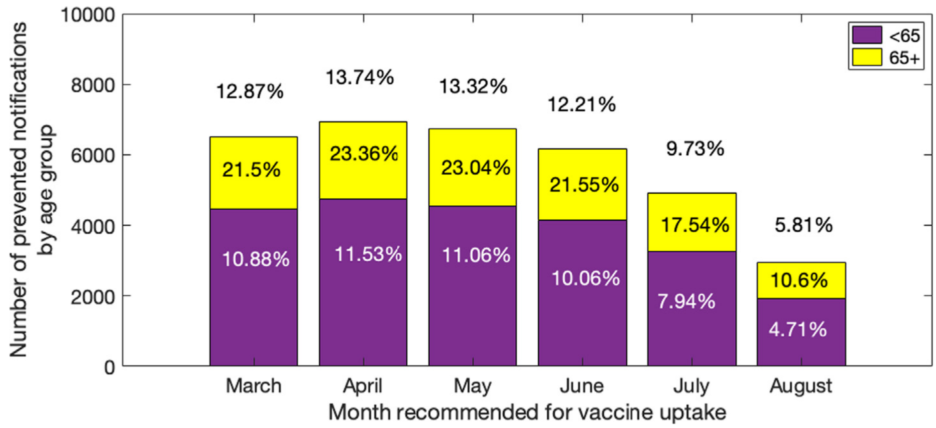

Fig. 6. Number and % of prevented cases by age group (<65 and 65 +) and total, by varying month of vaccination recommendation from March to August, with monthly distributed coverage in 9 months' time-window.

vaccination, if vaccination coverage remains constant. The average notification peak in Australia is in August, with early or late variation from this peak occurring occasionally. As such, a person vaccinated in March is facing a period of 5–6 months between vaccination and peak of influenza circulation. We found that vaccination protection starting to be effective in June and July will prevent the highest number of cases, however considering that it requires about 2 to 3 weeks for immunological response to the vaccine, May is the optimal time to get vaccinated in Australia, which is 2–3 months later than the usual recommended time for vaccination and 2 months before the seasonal peak. However, if delaying vaccination results in missed vaccinations and decrease coverage, delaying vaccination could have a net negative impact. Furthermore, if a time- gap is considered between vaccination recommendation and uptake, earlier recommendation is more effective.

Importantly, we did not find a large difference in cases prevented between months of vaccination and if coverage drops by 5% for the 65+ and 2% for the <65 per months, earlier vaccination prevents more cases. A recommendation to delay vaccination should not be taken lightly, as this may reduce vaccine coverage, and may the vaccine uptake is delayed from the recommendation month. In addition, for individuals at high risk of complications of influenza, if delay increases the risk of missing or forgetting vaccination altogether, it is preferable to get vaccinated as soon as feasible.

Waning varies by strain of influenza, with the least waning observed with A(H1N1). During a predominant A(H1N1) season [31], there is unlikely to be any benefit to delaying vaccination. The benefits of delaying would be increased for predominant A (H3N2) seasons, which demonstrates the most waning [37]. However, it is unlikely to be practical to make decisions on timing during an unfolding season, based on the predominant strain.

There are some limitations to this study. While the results are particularly sensitive to the monthly waning, it should be noted that the evidence around waning is not extensive, subject to uncertainty and with inconsistent results across time from vaccination, age and influenza strain. Most studies which have examined waning found decreased effectiveness after 3–6 months from vaccination [17,27,31], however the amount of waning found was more than 36% in Europe [27] and less than 20% in Australia and UK [17]. In the US, one study found that risk of influenza increased 12% for every two weeks since vaccination [25], whilst another found only a small reduction in vaccine effectiveness starting from 6 months from vaccination [34]. Furthermore, we assumed a linear dependency between vaccine effectiveness and time from vaccination, however it is not known the relationship between the two.

We used annual coverage data for each age group, but it would have been more accurate if Australian monthly coverage was used, however these data are not available in Australia. VE data used in the model is based largely on the performance of standard trivalent inactivated influenza vaccines (TIVs) which were the predominant vaccines used till 2015. From 2016 quadrivalent influenza vaccines (QIVs) replaced TIVs [42] in Australia, which have better vaccine effectiveness. Furthermore, results are shown for an average between 9 seasons and an individual influenza season can vary considerably in strain prevalence. Furthermore, from 2018 high dose and adjuvanted TIV were registered and funded for 65+ instead of standard TIV, which improves protection against influenza in older people [43].

This study has several strengths. We estimated the waning function specifically for each year based on the proportion of each strain circulating over 9 years, so that we could estimate an averaged waning effect. We analysed two age groups have different coverage separately. There are no previous studies that have modelled timing of vaccination but a study that looked at vaccine waning [24] found that delayed vaccination achieved higher protection during the season.

Finally, although this study suggests that administering influenza vaccine closer to the peak of the season may give higher overall protection for the entire season, influenza seasons can vary considerable in length, start and peak time, which makes it difficult to estimate the exact time to be vaccinated. The percentage of prevented cases between vaccination scenarios varies only of 2.27% between the lowest and the highest effective month, which suggests careful consideration of risk and benefit of delaying vaccination. To implement a flexible, responsive vaccination timing policy would require excellent and highly sensitive early season influenza surveillance and predictive tools to forecast the predominant strain and severity of a given season and most importantly it will require an effort to keep high coverage rates if the time window for vaccine uptake is shortened. This area needs further investigation, and research is required on intraseasonal VE waning for QIVs and high dose TIVs using age specific and monthly coverage data, to inform any potential changes to current vaccine recommendations.

In conclusion this study found that, delaying vaccine uptake to May/June, when considering vaccine effectiveness waning, will prevent more influenza cases, however if coverage decreases earlier uptake is more effective. Furthermore, vaccine uptake not essentially corresponds with vaccine recommendation, indeed if a time gap is considered between the two, delaying the recommendation month for vaccination can have a negative impact on the number of cases prevented.

Ethics approval

An ethical approval for this study was not required.

Transparency declaration

I, Valentina Costantino, declare that the manuscript is an honest, accurate and transparent account of the study being reported; that not important aspects of the study have been omitted; and that there are not any discrepancies from the study as original planned.

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This research has been funded from Seqirus Australia, the funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Summary

Vaccine effectiveness has been found to wane over a season, therefore we aimed to estimate the most effective vaccination time for an average Australian influenza season. Our study suggests that, if the coverage remains constant, delaying vaccination to May/June will prevent more cases overall the influenza season in Australia. However, if coverage decreases or a time gap is considered between vaccine recommendation and actual uptake, delaying recommendation can have a net negative impact.

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.

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