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Evaluating the effectiveness of the influenza vaccine during respiratory outbreaks in Singapore's long term care facilities, 2017

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ABSTRACT

Influenza outbreaks occur periodically in Long Term Care Facilities (LTCFs) and vaccination is critical in preventing influenza infections. We evaluated the influenza vaccine effectiveness (VE) during respiratory outbreaks in LTCFs reported to the Ministry of Health, Singapore in 2017.

A test-negative design was used to estimate the ratio of the odds of testing positive for influenza among vaccinated individuals to the odds among unvaccinated individuals. The VE was calculated as (1-odds ratio) × 100%. For adjusted VE, the estimates were derived using logistic regression adjusted for age group, gender, month of illness, and number of days from date of illness onset till to swab collection date. Estimates by influenza subtypes and post-vaccination time periods (15–180 days & 181–365 days) were also calculated using stratified data.

264 individuals, with 118 laboratory-confirmed influenza cases [32 A(H1N1)pdm09, 75 A(H3N2), 11 A (untypable)], were included in the analysis. No one was identified to be infected with influenza B. The overall adjusted VE estimate was 40.5% (95% CI: −12.2–68.5%), while the subtype-specific adjusted VE estimates were −43.4% (95% CI: −312.4–50.2%) against A(H1N1)pdm09 and 57.1% (95% CI: 5.7–80.5%) against A(H3N2). At 15–180 days post-vaccination period, the adjusted VEs were 59.3% (95% CI: 18.0–79.8%) against all influenza, 35.4% (95% CI: −123.5–81.3%) against A(H1N1)pdm09 and 67.9% (95% CI: 22.5–86.7%) against A(H3N2). Estimates were not significant at 181–365 days post-vaccination.

The influenza vaccine showed varying effectiveness among individuals in Singapore's LTCFs in 2017, with a higher effectiveness among those who were more recently vaccinated. It remains an important tool in preventing influenza infections, especially for those who are at high risk of influenza-related complications.

1. Introduction

Singapore is a city state located near the equator and experiences year-round influenza activity [1]. Two periods of higher influenza activity usually occur in the beginning and middle of the year, coinciding with the northern and southern hemisphere winter seasons respectively [2].

Long Term Care Facilities (LTCFs) in Singapore provide services to individuals and seniors who require social assistance, or may be frail and need support with their activities of daily living in institutionalised settings [3]. They report outbreaks of infectious diseases among their residents and/or staff to the Ministry of Health (MOH), Singapore, when the pre-defined conditions for reporting are met [4] or further assistance from MOH is required. The MOH offers assistance to affected LTCFs to investigate the outbreak, including the identification of causative pathogen(s) such as influenza through laboratory testing, and to provide advice on additional infection prevention and control measures.

Influenza vaccination is an important tool in preventing influenza infections [5]. The MOH recommends annual influenza vaccination for those who are at increased risk of influenza-related complications, including persons aged ≥65 years and residents of long term care facilities [6]. Circulars on influenza vaccinations

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are sent semi-annually to key vaccination providers in the healthcare sector, including medical practitioners, healthcare institutions and LTCFs, before the beginning of southern and northern hemisphere influenza seasons. Vaccination may be recommended up to twice a year depending on changes to the vaccine composition to protect against circulating influenza viruses [7].

Influenza vaccine effectiveness varies across influenza seasons, as well as age groups, depending on the degree of matching between the influenza virus strains in the vaccine and the circulating strains in that particular season [8]. Previous studies have also reported waning effectiveness after a period of time, which can be as early as 100–119 days after vaccination [9–13]. The objectives of this study were to derive estimates for the effectiveness of the influenza vaccine from respiratory outbreak investigations in Singapore's LTCFs in 2017, and to derive separate estimates for people who were vaccinated 15–180 (about less than half a year) and 181–365 days (within one year) prior to illness onset.

2. Methods

2.1. Study design

Our study retrospectively examined the outbreaks in LTCFs that occurred between 1st January and 31st December 2017. Individuals were defined as cases if they had been diagnosed with laboratory-confirmed influenza and as controls if otherwise, and included both residents and staff of LTCFs. Individuals were considered vaccinated if they were administered with any influenza vaccine 15–365 days prior to illness onset. Individuals vaccinated $\leq$14 days prior to illness onset were removed from the study, as adequate immune response to the vaccine might not be present. Other than individuals who were identified in records as being unvaccinated, individuals with missing information on vaccination statuses were also assumed to have no prior vaccination.

We also plotted the weekly influenza activity data from the MOH's national influenza surveillance programme with the weekly incidences of cases/controls to check for correlations.

2.2. Laboratory diagnosis and data collection

When LTCFs report respiratory outbreaks, the MOH deploy officers to conduct epidemiological investigations under the Infectious Diseases Act (IDA). This includes collecting random specimens of nasopharyngeal or throat swabs from individuals who develop influenza-like illness (ILI) symptoms recently or are currently symptomatic. Respiratory samples from outbreaks that occurred in 2017 were sent to the National Public Health Laboratory (NPHL) for testing of influenza and other respiratory pathogens using FilmArray Respiratory Panel (version 1.7) [14].

Data collected include personal particulars (age, gender), presenting symptoms (e.g. fever, cough, sore throat and runny nose), temperature measurements, date of illness onset, influenza vaccination history (date of last vaccination, brand and batch number of the vaccine), mode of medical treatment (outpatient treatment or hospitalisation), positive respiratory pathogens detected, and outcome (recovered or died). LTCFs provided influenza vaccination status of cases through in-house vaccination records or through residents' personal medical records if the vaccinations were provided elsewhere.

2.3. National surveillance programme for influenza viruses

As part of the national surveillance of influenza activity, virological surveillance of influenza viruses is carried out on throat and/or nasopharyngeal specimens obtained from government primary care centres (polyclinics), hospitals and sentinel general practitioner clinics throughout the year. Specimens collected from 2017 were sent to the NPHL and designated hospital laboratories for the typing, subtyping and isolation of influenza viruses. The 4-week moving influenza positivity was calculated by using the proportion of samples that had been laboratory-confirmed positive for influenza from the current week and preceding 3 weeks. Further genomic analysis and antigenic characterisation of selected samples collected from January to June 2017 were conducted by NPHL and the WHO Collaborating Centre for Reference and Research on Influenza, Melbourne, Australia.

2.4. Statistical model

A test-negative design (TND) was used to estimate the ratio of the odds of testing positive for influenza among vaccinated individuals to the odds among unvaccinated individuals. The TND has been found to control for differences in healthcare-seeking behaviour between the vaccinated and unvaccinated groups, where unequal probabilities of getting laboratory-tested for influenza can be a potential confounder [15–17]. The vaccine effectiveness (VE) was calculated as

$$VE = (1 - OR) * 100\%$$

where OR is the odds ratio [15]. For adjusted VE, the odds ratio was estimated using logistic regression adjusted for age group (<50, 50–64, 65–79 and $\geq$80 years), gender, number of days from date of illness onset till date of sample collection and calendar month. Controlling for calendar time has been found to be essential for influenza VE assessment, especially in regions that experience year-round influenza activity [16]. The type of vaccine formulation was not included as a variable due to incompleteness of data. LTCF site was also not included as a variable due to correlation with calendar month (Supplementary Table S1). Estimates by influenza subtype and post-vaccination time periods (15–180 days & 181–365 days) were calculated using stratified data. As a sensitivity analysis, VE estimates were derived using a mixed effects model with calendar month as a random intercept.

Selected characteristics of those who tested positive for influenza and those who tested negative were compared by Chi-square test, or Fisher's Exact Test where appropriate. P values under 0.05 were considered statistically significant. Analyses were carried out in the R statistical software version 3.3.1 [18].

3. Results

Based on the MOH's outbreak investigations, 1006 LTCF residents or staff were involved in 26 respiratory outbreaks in 2017 that occurred in 20 different sites, with 4 sites reporting multiple outbreaks over the year. Respiratory samples were taken from a total of 282 individuals. Of these, 18 individuals were excluded from the analysis because they were either vaccinated <14 days before illness onset or they had incomplete data. 264 individuals, whose dates of onset ranged from 11th January 2017 to 30th November 2017, were therefore included in the final analysis, comprising of 146 (55.3%) controls and 118 (44.7%) cases (Table 1).

83 (56.9%) controls and 56 (47.5%) cases were classified as having been vaccinated based on the study criteria. Almost all of the vaccinated individuals (95.7%) were identified to be administered with the inactivated influenza vaccine (brand names Fluarix, FluQuadri, Influvac, Vaxigrip), while the rest were unidentified. Individuals included in the final analysis had ages ranging from 18 to 104 years, and 20 (7.6%) of them were staff belonging to the LTCFs. Cases had a higher proportion of 65–79 year old individuals but a lower proportion of $\geq$80 year old individuals. There was a higher

Table 1
Descriptive characteristics of the studied individuals (n = 264).

	Flu-negative controls (n = 146)		Flu-positive cases (n = 118)		P-value
	No.	%	No.	%	
Age group (years)					<0.01
<50	31	21.2	21	17.8	
50–64	53	36.3	48	40.7	
65–79	24	16.5	35	29.6	
80+	38	26	14	11.9	
Gender					0.04
Female	74	50.7	45	38.1	
Male	72	49.3	73	61.9	
Ethnic group					0.45
Chinese	115	78.8	88	74.5	
Indian	10	6.8	10	8.5	
Malay	15	10.3	10	8.5	
Others	6	4.1	10	8.5	
Resident/Staff					0.36
Resident	133	91.1	111	94.1	
Staff	13	8.9	7	5.9	
Vaccination status					0.01
Not vaccinated	63	43.1	62	52.5	
15–180 days	68	46.6	35	29.7	
180–365 days	15	10.3	21	17.8	
Influenza subtyping					–
Negative	115	78.8	–	–	
Other respiratory viruses	31	22.2	–	–	
A(H1N1)pdm09	–	–	32	27.1	
A(H3N2)	–	–	75	63.6	
A not subtyped	–	–	11	9.3	
Days from illness onset till swab collection					0.01
0–2	68	46.6	70	59.3	
3–4	31	21.2	31	26.3	
5–6	31	21.2	12	10.2	
>7	16	11.0	5	4.2	
Month of onset					<0.01
January	5	3.4	10	8.5	
February	3	2.1	0	0.0	
March	26	17.8	0	0.0	
April	4	2.7	8	6.8	
May	25	17.1	47	39.8	
June	50	34.3	35	29.7	
July	8	5.5	8	6.8	
August	0	0.0	0	0.0	
September	19	13.0	3	2.5	
October	2	1.4	0	0.0	
November	4	2.7	7	5.9	
December	0	0.0	0	0.0	
Site number					<0.01
1	4	2.7	8	6.8	
2	0	0.0	2	1.7	
3	18	12.3	6	5.1	
4	6	4.1	7	5.9	
5	15	10.3	11	9.3	
6	11	7.5	0	0.0	
7	12	8.2	7	5.9	
8	5	3.4	8	6.8	
9	5	3.4	5	4.2	
10	5	3.4	4	3.4	
11	5	3.4	0	0.0	
12	1	0.7	9	7.6	
13	0	0.0	13	11.0	
14	0	0.0	1	0.8	
15	0	0.0	3	2.5	
16	39	26.7	15	12.7	
17	3	2.1	5	4.2	
18	3	2.1	3	2.5	
19	4	2.7	11	9.3	
20	10	6.8	0	0.0	

*Sites 3, 4, 5 and 7 have >1 outbreak.

proportion of males in cases than controls (61.9% vs 49.3%). Cases were also more likely to have their swab specimen collected closer to the date of onset, as 59.3% of cases had their specimen collected within 2 days compared to 46.6% in controls.

Out of the 118 cases, 32 (27.1%) cases tested positive for influenza A(H1N1)pdm09 and 75 (63.6%) were infected with A(H3N2), while the remaining 11 (9.3%) tested positive for influenza A but were not subtyped due to low viral titre. No one was identified to be infected with influenza B. The majority (83.1%) of the cases had influenza infections in the months of April to July which generally coincided with the southern hemisphere influenza season. The number and size of respiratory outbreaks corresponded to higher influenza activity from the community-based national influenza virological surveillance programme (Fig. 1).

The overall adjusted vaccine effectiveness observed in LTCFs during the study period was estimated to be 40.5% (95% Confidence Interval (CI): −12.2–68.5%; p-value = 0.11) (Table 2). Stratified analyses of different post-vaccination periods showed a higher VE of 59.3% (95% CI: 18.0–79.8%; p = 0.01) for 15–180 days, as compared to an estimated VE of −10.2% (95% CI: −173.4–55.5%; p = 0.83) for 181–365 days.

Subtype-specific analyses showed that the adjusted VE estimate against influenza A(H3N2) was 57.1% (95% CI: 5.7–80.5%; p = 0.04), while that against influenza A(H1N1)pdm09 was estimated to be −43.4% (95% CI: −312.4–50.2%; p = 0.50). Similar to the VE estimates against all influenza, the influenza subtype-specific VE was higher in people who had more recent vaccinations. The adjusted VEs against influenza A(H3N2) and A(H1N1)pdm09 were 67.9% (95% CI: 22.5–86.7%; p = 0.01) and 35.4% (95% CI: −123.5–81.3%; p = 0.49) respectively during the 15–180 days post-vaccination period. VE estimates for the 181–365 post-vaccination periods were not significant. Results from the mixed effects model showed little difference in results.

4. Discussion

Our study provides novel data on influenza vaccine effectiveness in the tropics. In our study, the influenza vaccine was found to have provided a low to moderate amount of protection to individuals in LTCFs during respiratory outbreaks in 2017. VE estimates were statistically significant for all influenza (15–180 days) and influenza A(H3N2) (15–365 days & 15–180 days).

The estimated VE of 40.5% was comparable to published estimates for the 2016–2017 northern hemisphere influenza season from studies using test-negative designs. During the 2016–17 season, the VE was estimated to be 48% (95% CI: 37–57%) (interim) in the United States (US) and 39.8% (95% CI: 23.1–52.8%) in the United Kingdom (UK) [19,20]. A lower interim VE of 33% (95% CI: 17–46%) was estimated in Australia during the southern hemisphere season from May to September 2017 and sequential vaccination with identical vaccine composition across consecutive seasons was cited as a contributing factor to the low VE estimate [21].

In our study, the adjusted VE against influenza A(H3N2) was 57.1%, higher than the estimates ranging from 10% to 43% reported in the US, UK and Australia [19–21]. The discrepancies between these studies were probably due to the varying co-circulating A (H3N2) subclusters in the different countries. From further genomic and antigenic analyses of surveillance samples collected from January to June 2017, all A(H3N2) samples sequenced (n = 201) belonged to the major clade 3C.2a, of which 88% fell within the emergent subclade 3C.2a1 with at least 4 co-circulating subclusters. Hemagglutinin inhibition assays suggested that viruses belonging to clade 3C.2a1 were antigenically related to the vaccine component A/Hong Kong/4801/2014 (H3N2), although other studies have cautioned that antibodies raised against representative cell-culture propagated viruses from some 3C.2a1 subclusters reacted poorly to egg-propagated A/Hong Kong/4801/2014 [22]. In our study, vaccinated enrolees were administered with the influenza vaccine from May 2016 to August 2017. This time period coincided with the commercial availability of the 2016 Southern Hemisphere (SH), 2016/17 Northern Hemisphere (NH) or 2017 SH vaccines, all of which included A/Hong Kong/4801/2014 (H3N2) [22] (Table 3).

VE estimates for influenza A(H1N1)pdm09 tend to be higher than estimates for influenza A(H3N2) after the 2009 influenza pandemic due to antigenic drift properties seen in influenza A(H3N2) viruses [23]; however, the adjusted VE estimate for influenza A

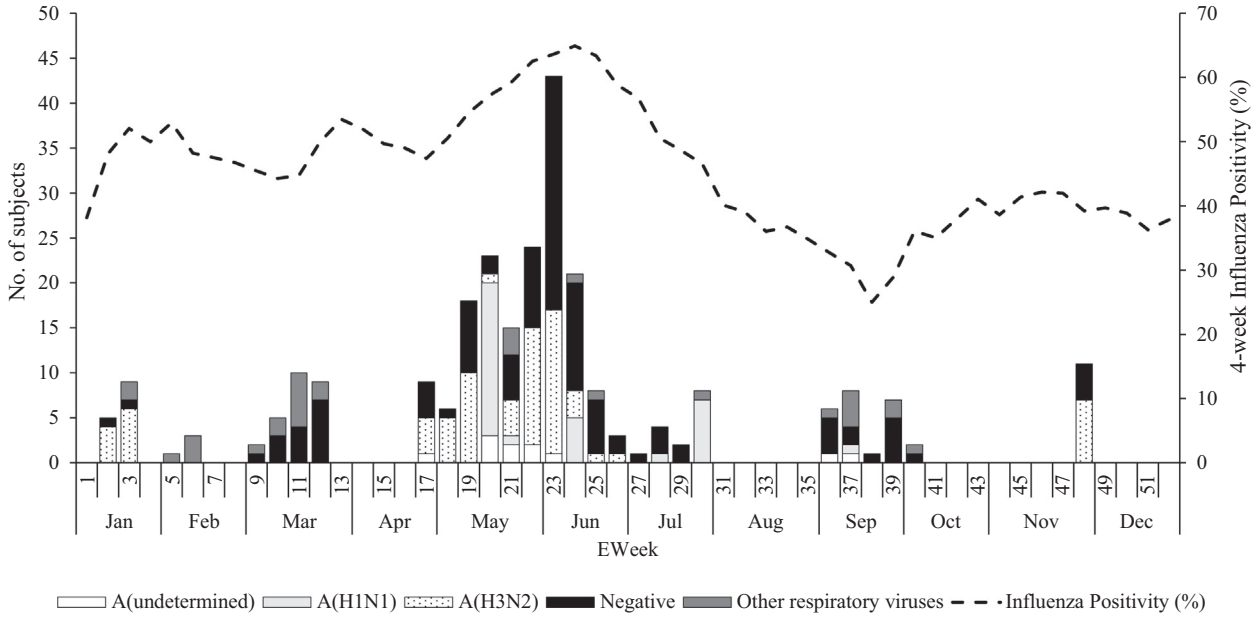

Fig. 1. Epidemic curve of individuals included in the final analysis by epidemiology weeks and 4-week influenza positivity (%) from national influenza surveillance programme, 2017.

Table 2
Crude and adjusted estimates of influenza vaccine effectiveness (VE) by sub-type and post-vaccination periods.

	No. of controls	No. of cases	Crude VE			Adjusted VE*		
			%	95% CI	p-value	%	95% CI	p-value
Overall								
Not vaccinated	63	62	Reference	–	–	Reference	–	–
Vaccinated 15–365 days	83	56	31.4	−11.6–57.9	0.13	40.5	−12.2–68.5	0.11
Vaccinated 15–180 days	68	35	47.7	10.5–69.5	0.02	59.3	18.0–79.8	0.01
Vaccinated 181–365 days	15	21	−42.3	−201.0–32.8	0.36	−10.2	−173.4–55.5	0.83
A(H1N1)pdm09								
Not vaccinated	63	14	Reference	–	–	Reference	–	–
Vaccinated 15–365 days	83	18	2.4	−111.1–54.9	0.96	−43.4	−312.4–50.2	0.50
Vaccinated 15–180 days	68	9	40.4	−47.2–75.9	0.26	35.4	−123.5–81.3	0.49
Vaccinated 181–365 days	15	9	−170.0	−640.1–1.6	0.05	−280.8	−2994.2–53.1	0.21
A(H3N2)								
Not vaccinated	63	40	Reference	–	–	Reference	–	–
Vaccinated 15–365 days	83	35	33.6	−16.2–62.0	0.15	57.1	5.7–80.5	0.04
Vaccinated 15–180 days	68	25	42.1	−6.1–68.4	0.08	67.9	22.5–86.7	0.01
Vaccinated 181–365 days	15	10	−5.0	−156.4–57.0	0.91	19.5	−154.8–74.5	0.71

* Adjusted for age group, gender, days from illness onset to swab collection and calendar month.

Table 3
Recommended vaccine formulations for influenza seasons in 2016 and 2017 and main circulating influenza viruses in the community from January to June 2017.

Influenza type/subtype	Vaccine formulation			Circulating strains in Community (Jan-Jun 2017)
	2016 Southern Hemisphere	2016/17 Northern Hemisphere	2017 Southern Hemisphere	
A(H1N1)pdm09	A/California/7/2009(H1N1)pdm09		A/Michigan/45/2015 (H1N1) pdm09	A/Michigan/45/2015 (H1N1)pdm09
A(H3N2)	A/Hong Kong/4801/2014 (H3N2)		A/Hong Kong/4801/2014 (H3N2)	A/Hong Kong/4801/2014 (H3N2)
B	B/Brisbane/60/2008		B/Brisbane/60/2008 B/Phuket/3073/2013	B/Brisbane/60/2008 B/Phuket/3073/2013

(H1N1)pdm09 in our study was lower than that for influenza A (H3N2). A possible reason is that, from the antigenic characterisation results, the circulating influenza A (H1N1)pdm09 viruses in the first half of 2017 were from the phylogenetic subclade 6B.1 and likely contained strains with emerging antigenic differences from the 2016 SH and 2016–2017 NH vaccine component A/California/7/2009(H1N1)pdm09, which belonged to clade 6B. 106 out of the 139 (76.3%) vaccinated individuals in our study were vaccinated before the updated 2017 SH vaccine (comprising A/Michigan/45/2015(H1N1)pdm09) became available in April, hence few would be optimally protected against the eventual circulating strain from April to June 2017. This finding is consistent with the WHO's recommendation of administering the most recent vaccine formulations in tropical and subtropical countries [24]. Another possible reason for the lower VE might be a baseline level of immunity among studied individuals against A(H1N1)pdmn09, which had been antigenically stable since 2009 [22]. The immunity could be acquired through either natural infection or prior routine immunisations, which was likely in the context of LTCFs. Hence, the observed differences between vaccinated and non-vaccinated individuals in our study might be diminished since the non-vaccinated individuals could already have had significant prior immunity towards influenza A(H1N1)pdm09.

It should be noted that the methodology described in this paper differs from other studies in that we used outbreak data from enclosed environments catered for individuals with certain characteristics (i.e people who were frailer or older), instead of data from outpatient visits where patients were more representative of the general community. This could also explain why our VE estimates, especially the subtype-specific ones, differed from the estimates reported in other countries. Foppa IM et al had previously found that TND studies might overestimate influenza VE in inpatient settings, due to the over-representation of vaccinated controls [25]. For example, they highlighted that individuals with chronic conditions such as chronic obstructive pulmonary diseases had higher vaccination rates, while simultaneously having increased probabilities of being hospitalised from non-infectious respiratory diseases. These individuals might then be enrolled in inadequately designed hospital-based TND studies as vaccinated controls. In Singapore, the MOH recommends influenza vaccination for all persons receiving intermediate and long term care services [6], hence we do not anticipate any difference in vaccine coverage between the controls and the overall LTCF population in our study. Baseline immunity levels in LTCF settings might also affect the VE estimates, as described in the previous paragraph. Further studies should be conducted to validate the TND in LTCFs.

In our study, stratified analyses yielded higher VE estimates in individuals who were more recently vaccinated, corroborating the findings from other studies reporting waning effectiveness of influenza vaccine over time [9–13]. Two recent meta-analyses, one based on TND case-control studies and the other based on studies reporting hemagglutination-inhibition (HI) antibody responses, concluded that influenza vaccine protection might not persist throughout the year and alternatives to annual influenza vaccination schedules, or new vaccines with improved immunogenicity, should be explored in countries with year-round influenza activity [9,10]. While our study did lend credence to the notion that a single annual dose might not be sufficient, our analysis did not study evidence to support the increased frequency of influenza vaccination due to lack of data on sequential vaccinations. Another consideration is that that the waning effect might be overstated by the TND because of the natural immunity being attained by the control group over time [26]. It should also be noted that our estimates from the two time periods were not statistically different if inferred from the overlapping confidence intervals. This was most probably due to the small sample size,

especially for the 180–365 days post-vaccination period. Analyses similar to our current study should be continued and extended to the community settings to assess whether the waning protection of annual influenza vaccination have effects on the local population.

4.1. Limitations and strengths

One limitation was the small sample size which affected the precision of the VE estimates as seen in the wide confidence intervals. WHO recommends a sample size of at least 109 cases, assuming a VE of 70% with precision level of 20% [17]. The dataset also had incomplete information on prior seasons' vaccinations, individuals' underlying chronic conditions and the types of vaccine formulation administered, all of which might affect the VE estimates and subsequent interpretations. Ohmit et al had previously reported that prior years' vaccinations might reduce the VE of the current year [27]. This study also did not distinguish VE estimates for separate influenza seasons and their corresponding vaccine formulations due to the year-round influenza activity observed in Singapore. The impact of the vaccine against influenza-associated hospitalisations was also not analysed due to the small number of hospitalisations (only 60) in the dataset. Collection of data on chronic conditions could be considered for future studies.

An advantage of our study was that participants were institutionalised individuals with vaccination statuses obtained from vaccination records, and not through self-reporting which would had been subjected to recall bias. This would improve the reliability of the VE estimates. As individuals from the same site were confined in the same area, the degree of exposure to the influenza virus should also be similar among the vaccinated and unvaccinated groups.

5. Conclusions

Our study found varying effectiveness of the influenza vaccine among individuals residing in Singapore's LTCFs in 2017. While annual vaccination strategies remain of value, higher effectiveness was observed in people who were more recently vaccinated, thus indicating a possible waning effect across the period of a year. Actual vaccine benefits depend on the circulating influenza strains and high risk groups should be given the most updated vaccine to protect against influenza infections and its complications.

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Conflicts of interest

None declared.

Authors' contributions

Conceived the analysis: VL, LC, YN, KN.
Collection and cleaning of data: YN, KN, KF, IM, CL.
Analysed the data: YN, LC, SM.
Wrote the paper: YN, KN, TM, LC, SM, RL, SO, LJ, VL.

All authors attest they meet the ICMJE criteria for authorship.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.03.054.

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