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Comparing influenza vaccine effectiveness between cell-derived and egg-derived vaccines, 2017–2018 influenza season

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ABSTRACT

The Department of Defense Global Respiratory Pathogen Surveillance Program conducted a study to compare the differences in vaccine effectiveness (VE) of the cell-derived and egg-derived vaccines. DoD healthcare beneficiaries, excluding service members, that presented with influenza-like illness for the period of 1 October 2017 through 28 April 2018 were included in a test-negative case-control study examining laboratory confirmed influenza infections. Three VE analyses were performed (1) influenza infection among those vaccinated with cell-derived vaccines (2) influenza infection among those vaccinated with egg-derived vaccines and a (3) relative VE which directly compared the odds of influenza infection with cell-derived vaccine against those with egg-derived vaccines. The cell-derived and egg-derived vaccines were moderately protective against all influenza types with significant VE estimates for all dependents at 46% (95% confidence interval, 33, 56) and 53% (45, 60), respectively. Of the subtype analyses, influenza A(H1N1)pdm09 performed the best. In the cell-derived vaccine, the adult age group was moderate to high at 71% (44, 85) and children moderate at 56% (15, 75). In the egg-derived vaccine, the children age group was at a high 88% (80, 93) effectiveness and adults at 81% (56, 92). When comparing cell-derived vaccine directly to the egg-derived vaccine, the relative VE found significant results only for influenza A(H1N1)pdm09 which favored the egg-derived vaccine with odds ratios of 2.0 (1.1, 3.6) for all dependents and 2.9 (1.3, 6.3) for children. In the influenza A(H3N2) analysis, statistical significance was not gained; however, the odds favored the cell-derived vaccine.

1. Introduction

The effectiveness of the influenza vaccine varies each season due to the unpredictability of the influenza virus. The constant antigenic drifts and potential antigenic shifts that the virus undergoes makes it difficult to predict which strain will predominate in the next season. Antigenic drift is the process by which small changes in the genes for surface proteins, hemagglutinin (HA[1]) and neuraminidase (NA), gradually mutate over time. Antigenic shift is the process by which a new HA and/or NA lineage replaces a currently circulating strain, exposing the population to new antigenic diversity [1]. The resulting antigenic changes are the cause for global surveillance and the need for an annual vaccine. The United States Air Force School of Aerospace Medicine's (USAFSAM) Department of Defense (DoD) Global Respiratory Pathogen Surveillance (DoDGRS) program's mission is to perform worldwide respiratory pathogen surveillance and calculate influenza vaccine effectiveness (VE) for DoD dependents at sentinel and participating sites. The influenza data, which is collected throughout the season, is provided to the Food and Drug Administration's Vaccines and Related Biological Products Advisory Committee meeting for strain selection for the vaccine in late February or early March.

During the 2017–2018 season, the DoDGRS annual midseason adjusted VE showed a low overall estimate for influenza A(H3N2) at 37% (95% confidence interval (CI), 22, 49) [2]. The United States (US) Centers for Disease Control and Prevention (CDC)

Abbreviations: AF, Air Force; AFCITA, Air Force Complete Immunization Tracking Application; CDC, Centers for Disease Control and Prevention; CI, confidence interval; CVV, Candidate Vaccine virus; DoD, Department of Defense; DoDGRS, Department of Defense Global Respiratory Pathogen Surveillance; HA, hemagglutinin; IRB, Institutional Review Board; LRMC, Landstuhl Regional Medical Center; MDCK, Madin-Darby Canine Kidney; MTF, military treatment facility; NA, neuraminidase; OR, odds ratio; RT-PCR, reverse-transcription polymerase chain reaction; US, United States; USAFSAM, United States Air Force School of Aerospace Medicine; VE, vaccine effectiveness; WPAFB, Wright-Patterson Air Force Base.

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also showed low adjusted VE results at 25% (13, 36) for influenza A(H3N2) [3]. The low VE estimates were expected after Australia had a low VE at 10% for an influenza A(H3N2) predominant season during the 2017 Southern Hemisphere's interim season results [4]. The low VE estimates were not primarily attributable to antigenic mismatch but potentially from altered antigenicity in the egg-propagated vaccine, as shown by recent antigenic characterization of the egg-propagated vaccine viruses [4]. Researchers have found that efficacy can be reduced during the vaccine production of the egg-derived vaccine where substitutions occur on the HA glycoprotein which changes the antigenicity due to multiple virus passages [5]. For example, according to Wu et al. (2017), the annual influenza VE has been declining over the years, especially for the A(H3N2) component due to an egg-adaptive substitution (L194P) which dramatically changes the HA antigenicity [5]. The DoDGRS among other organizations started assessing the difference in the effectiveness of the cell-derived vaccine and the egg-derived vaccine based on the low VE estimates for influenza A(H3N2).

For approximately 50 years, egg-derived vaccines have been the predominant method used for generating hundreds of millions of influenza vaccines each year. This manufacturing strategy uses the HA and NA genetic segments from currently circulating influenza strains and creates reassortant viruses that are grown in embryonated chicken eggs and screened to isolate "candidate vaccine viruses" (CVVs) [6]. Regardless of vaccine strain or manufacturing platform, the influenza vaccines are typically produced by growing target viruses in chicken eggs, which requires an abundant egg supply [1]. The cell-derived vaccine is manufactured in a similar way where the HA and NA reassortant viruses are grown in mammalian cells, in liquid culture [6]. Cell production has been successful in cell lines like the Madin-Darby Canine Kidney (MDCK) cells, monkey kidney cells, and human embryonic retinal cells which have been approved in the US and Europe since 2009 [1]. New vaccine platforms are being developed to improve the vaccine production, availability, and to improve immune response [1].

In order to assess the VE differences among the vaccines, the DoDGRS performed two VE analyses (cell-derived versus unvaccinated and egg-derived versus unvaccinated) and a relative VE analysis (cell-derived versus egg-derived vaccine) to measure the performance of the two vaccine types. The DoD purchased more cell-derived vaccines than egg-derived vaccines for this season, which led to a hypothesis that the military population and the DoD dependents were more likely to be protected against influenza infection than individuals receiving the egg-derived vaccine. Of the DoD vaccines purchased, 57% were Flucelvax, which were cell-derived, and the remainder were FluLaval and Fluarix, which were egg-derived (Table 1) [7].

2. Methods

The population included DoD healthcare beneficiaries, but excluded service members, who presented to a military treatment facility (MTF) with an outpatient encounter for influenza-like illness (ILI) symptoms and had a respiratory specimen collected between 1 October 2017–28 April 2018 (weeks 40–17). The DoDGRS requested sentinel sites to submit 6–10 ILI specimens (using nasal wash or nasopharyngeal swab) a week with a self-reported questionnaire containing demographic, clinical, and vaccination history information. ILI was defined as an individual having (1) cough or sore throat and a fever $\geq$100.5°F within 72 h or (2) physician determined ILI. All specimens submitted are assumed to be from patients with an acute respiratory illness as the laboratory performs testing for clinical diagnostics, with the additional advantage of using the data for surveillance.

The Air Force Complete Immunization Tracking Application (AFCITA) was solely used to determine vaccination status and the type (cell-derived or egg-derived) of vaccine used while the self-reported questionnaire was primarily used to determine individuals who were unvaccinated (Table 2). AFCITA is a system utilized by Air Force (AF) MTFs to track immunizations largely for AF service members and their dependents, although other DoD dependents may be captured if they were vaccinated at an AF MTF. Individuals were considered immunized if they were vaccinated with one (cell-derived or egg-derived) vaccine at least 14 days prior to specimen collection. Individuals were considered unvaccinated if indicated on the self-reported questionnaire or had an influenza vaccine documented in AFCITA after their ILI medical encounter. All individuals less than six months of age, unknown vaccination status or type, any vaccine documentation errors, vaccinated <14 days prior to ILI encounter, or influenza coinfections were excluded from the analysis. Individuals were only included in the study once, regardless of the number of specimens submitted per individual.

A test-negative case-control study design was used to analyze the VE estimates for the cell-derived vaccine and the egg-derived vaccine. Patients were considered cases if there was a positive influenza result on reverse transcription polymerase chain reaction (RT-PCR) and/or viral culture. VE was calculated by comparing the odds of influenza-positive (cases) to influenza-negative (controls) patients among those vaccinated and unvaccinated. Three VE analyses were performed (1) influenza among those vaccinated with cell-derived vaccines (compared to unvaccinated controls) (2) influenza among those vaccinated with egg-derived vaccines (compared to unvaccinated controls) and a (3) relative VE which directly compared the odds of influenza with cell-derived vaccine against those with egg-derived vaccines. Multivariable logistic regression was used to calculate the odds ratios (OR) and 95%

Table 1
Influenza vaccine products purchased by the DoD for the 2017–2018 influenza season.

TYPE	Product	CVX	DoD Contracted Age Group	Age Indication	Total # of Doses	% Total Doses	Vaccine Type (% purchased)
Quadrivalent	FluLaval	150 (single dose)	6–35 mos	$\geq$6 mos	166,160[1]	5%	Egg - 43%
		158 (multiple vial)	$\geq$36 mos	$\geq$3 years	250,230[2]	7%	
	Fluarix	150 (single dose)	$\geq$36 mos	$\geq$3 years	1,079,150[1]	31%	
	Flucelvax	171 (single dose)	$\geq$9 years	>4 years	1,667,000[1]	48%	Cell - 57%
		186 (multiple vial)			327,610[2]	9%	
	Total				34,90,150		

CVX codes are developed and maintained by the CDC's National Center of Immunization and Respiratory Diseases and are used to identify specific vaccine products administered.

[1] 0.5 ml single dose prefilled syringe.

[2] Multidose vial; 5 ml; contains 10–0.5 ml doses.

Table 2
Distribution of influenza vaccine products administered to cases/controls during the 2017–2018 influenza season.

CVX	Frequency	% of Vaccine	Vaccine Description	Type
140	19	1.26	Influenza, seasonal, injectable, preservative free, trivalent	Egg
141	21	1.39	Influenza, seasonal, injectable, trivalent	Egg
151[1]	712	47.21	Influenza, injectable, quadrivalent, preservative free	Egg
158[1]	242	16.05	Influenza, injectable, quadrivalent	Egg
161	6	0.40	Influenza, injectable, quardrivalent, preservative free, pediatric, 0.25 ml	Egg
168	2	0.13	influenza, trivalent, adjuvanted	Egg
171[1,2]	379	25.13	Influenza, injectable, MDCK, preservative free, quadrivalent	Cell
186[1,2]	127	8.42	Influenza, injectable, MDCK, quadrivalent	Cell
N/A	2529	N/A	Unvaccinated	N/A

CVX codes are developed and maintained by the CDC's National Center of Immunization and Respiratory Diseases and are used to identify specific vaccine products administered. Of the 4037 cases and controls used in the analysis, this table shows the breakdown by vaccine product and whether the vaccine was manufactured using cell or egg-derived technology.
[1] DoD purchased vaccines.
[2] Although these vaccines are recommended for use in ages ≥4 years, the DoD requests these vaccines only be used in those ages ≥9 years in order to conserve the vaccine for the older age groups.

confidence intervals (CIs) using SAS/STAT® software version 9.4 (SAS Institute, Cary, NC, USA). VE was calculated by (1-OR) × 100%. Relative VE was represented by odds ratios and 95% CIs. Potential confounders were identified and controlled for in each logistic regression model. The backward elimination method was used to identify variable relevance based on overall statistical significance. The variables considered for adjustment were chosen a priori and included: age, geographic region, (Eastern US, Western US, and Outside Continental US) and month of illness (determined by specimen collection date). All VE analyses were performed by influenza subtype and stratified by age groups (≥6 months – 17 years, 18 years and older). Sensitivity analyses were conducted in order to assess seasonality differences of influenza among specimens collected in Europe and the US and selection of controls outside of the influenza season.

Laboratory testing was performed at USAFSAM Epidemiology Laboratory, Wright-Patterson Air Force Base (WPAFB), OH and Landstuhl Regional Medical Center (LRMC), Landstuhl, Germany. USAFSAM used RT-PCR and viral culture for influenza identification, while LRMC used RT-PCR only. The work performed through the Surveillance Program has been determined "Public Health Practice" and has an Institutional Review Board's (IRB) determination of "Not Human Use Research" therefore does not fall under the purview of an IRB. All work has been carried out ethically, and precautions were taken to protect individuals' identity and health data. This determination was made by the Air Force Research Laboratory IRB (29 April 2013; WPAFB, OH).

3. Results

During the 2017–2018 season, there were 11,124 respiratory specimens tested through week 17. Influenza activity peaked at a 50% positivity rate during week 52 and remained elevated until it began to decline in week 11 (Supplemental Fig. 1). After applying the exclusion criteria, the study included 4037 specimens, of which 1757 (43.5%) were confirmed influenza cases and 2280 test-negative controls. Both RT-PCR and viral culture tests were used for 77% (n = 3109) of the specimens. Approximately 23% (n = 927) were tested only via RT-PCR and one specimen was tested using viral culture only. Of those ran simultaneously on RT-PCR/viral culture, concordance of results was achieved in 92.7% of specimens. Discordant results were documented in 228 specimens with two specimens identified as positive via viral culture only. Of the specimens submitted 41.1% met the ILI case definition for symptoms and onset time, 42.4% were physician determined ILI, and the remaining 16.5% were unable to be categorized from lack of information. Of those with physician determined ILI, on average specimens were collected six days (7 day standard deviation) after symptom onset (Table 3). Of cases, 531 [30% (11% cell-derived and 19% egg-derived)] were vaccinated and 977 [43% (14% cell-derived and 29% egg-derived)] of controls were vaccinated. Overall, of the cases and controls 37% were vaccinated. USAFSAM performed testing on 3413 (85%) of the specimens, while LRMC performed similar testing and contributed 624 tested specimens. All specimens tested at LRMC originated from European countries.

The age range of the population was 0–94 years, with a mean of 24 years, median of 13 years, and mode of 1 year old. Gender was similar between cases and controls with 57% (n = 2307) of females comprising the population. Of the specimens tested, 80% were collected from the US, while the remaining 20% originated from Europe, the Middle East, and the Pacific Region. Of those vaccinated, 50% were vaccinated by November 2017 and 95% were vaccinated by the beginning of January. There were statistically significant differences (p-value < 0.05) between cases and controls by age group and month of illness. Gender, geographic region, vaccination month and vaccine type were all found insignificant with p-values > 0.05 (Table 3).

The overall VE in all dependents for the cell-derived and egg-derived vaccines were moderate at 46% (33, 56) and 53% (45, 60), respectively. When stratified by age group, children had lower VE in the cell-derived vaccine, 36% (12, 54), compared to the egg-derived vaccine, 55% (45, 64). Adults were slightly higher at 52% (36, 64) in the cell-derived vaccine and 51% (35, 63) in the egg-derived vaccine. Of the subtype analyses, influenza A(H1N1) pdm09 performed the best. In the cell-derived vaccine, the adult age group was moderate to high at 71% (44, 85) and children moderate at 56% (15, 75). In the egg-derived vaccine, the children age group was high at 88% (80, 93) effectiveness and adults at 81% (56, 92). Influenza A(H3N2) performed similarly across age groups with all dependents having moderate VE at 48% (30, 61) in the cell-derived vaccine. For the egg-derived vaccine, VE was low at 35% (20, 48) in all dependents, 35% (20, 48) in children, and 19% (-11, 41) for adults. Influenza B had the lowest VE with the cell-derived vaccine for all dependents at 40% (21, 55) effectiveness and moderate in the egg-derived vaccine at 53% (41, 63). All models were statistically significant except in the children age group of influenza B and adults of influenza A(H3N2) (Fig. 1, Supplemental Table 1). Additional information on the group sample size for each influenza subtype, vaccine type, vaccine status and population category for the cell-derived and egg-derived versus unvaccinated analysis can be found in Supplemental Table 2.

A direct comparison was made between the cell-derived vaccine and the egg-derived vaccine using the ORs from a relative

Table 3
Characteristics of participants in the VE study by outcome and vaccine type.

Characteristic		Cases (n = 1757) No. (%)	Controls (n = 2280) No. (%)	p-Value	Cell-derived (n = 506) No. (%)	Egg-derived (n = 1002) No. (%)	Unvaccinated (n = 2529) No. (%)
Gender	Female	994 (56.57)	1313 (57.58)	0.51862	299 (59.09)	527 (52.59)	1481 (58.56)
	Male	763 (43.42)	967 (42.41)		207 (40.91)	475 (47.41)	1048 (41.44)
Age	6 m-8	594 (33.80)	972 (42.63)	<0.0001	98 (19.37)	577 (57.58)	891 (35.23)
	9–17	373 (21.22)	334 (14.64)		89 (17.59)	126 (12.57)	492 (19.45)
	18–49	411 (23.39)	540 (23.68)		122 (24.11)	108 (10.78)	721 (28.51)
	50–64	261 (14.85)	269 (11.79)		100 (19.76)	93 (9.28)	337 (13.33)
	65+	118 (6.72)	165 (7.24)		97 (19.17)	98 (9.78)	88 (3.48)
Month of Illness	October	12 (0.69)	131 (5.75)	<0.0001	3 (0.59)	4 (0.40)	136 (5.38)
	November	24 (1.37)	189 (8.29)		12 (2.37)	28 (2.79)	173 (6.84)
	December	193 (10.98)	303 (13.28)		48 (9.49)	125 (12.48)	323 (12.77)
	January	709 (40.35)	582 (25.52)		142 (28.06)	338 (33.73)	811 (32.07)
	February	544 (30.96)	605 (26.53)		159 (31.42)	310 (30.94)	680 (26.89)
	March	219 (12.46)	351 (15.39)		107 (21.15)	157 (15.67)	306 (12.10)
	April	56 (3.19)	119 (5.22)		35 (6.92)	40 (3.99)	100 (3.95)
Geographic Region	Eastern US	842 (47.92)	1069 (46.89)	0.5896	287 (56.72)	454 (45.31)	1170 (46.26)
	Western US	575 (32.73)	766 (33.6)		126 (24.90)	344 (34.33)	871 (34.44)
	European/Middle East Region	268 (15.25)	366 (16.05)		82 (16.21)	122 (12.18)	430 (17.00)
	Pacific Region	72 (4.10)	79 (3.46)		11 (2.17)	82 (8.18)	58 (2.29)
Vaccination Status[1]	Vaccinated	531 (30.22)	977 (42.85)	<0.0001	506 (100)	1002 (100)	0 (0)
	Unvaccinated	1226 (69.77)	1303 (57.14)		0 (0.00)	0 (0.00)	2529 (100)
Vaccination Month	August	3 (0.56)	5 (0.51)	0.1697	0 (0.00)	8 (0.80)	0 (0)
	September	71 (13.37)	95 (9.72)		57 (11.26)	109 (10.88)	0 (0)
	October	194 (36.53)	359 (36.74)		130 (25.69)	423 (42.22)	0 (0)
	November	186 (35.02)	331 (33.87)		208 (41.11)	309 (30.84)	0 (0)
	December	56 (10.54)	129 (13.20)		90 (17.79)	95 (9.48)	0 (0)
	January	18 (3.39)	47 (4.81)		16 (3.16)	49 (4.89)	0 (0)
	February	3 (0.56)	11 (1.13)		5 (0.99)	9 (0.90)	0 (0)
Flu	A/not subtyped	2 (0.11)	0 (0)	<0.0001	0 (0.00)	2 (0.20)	0 (0)
	A(H1N1)pdm09	282 (16.05)	0 (0)		22 (4.35)	23 (2.30)	237 (9.37)
	A(H3N2)	779 (44.33)	0 (0)		82 (16.21)	182 (18.16)	515 (20.36)
	B	694 (39.49)	0 (0)		88 (17.39)	132 (13.17)	474 (18.74)
	Not Flu	0 (0)	2280 (100)		314 (62.06)	663 (66.17)	1303 (51.52)
Vaccine Type	Cell-derived	192 (36.15)	314 (32.13)	0.1144			
	Egg-derived	339 (63.84)	663 (67.86)				
ILI Criteria[2]	ILI Case definition	907 (22.47)	752 (18.63)	<0.0001			
	Physician determined ILI	634 (15.70)	1076 (26.65)				
	Unknown	216 (5.35)	452 (11.20)				

[1] Vaccination status was determined by electronic medical records and plausible self-report at enrollment. Individuals were considered vaccinated if at least one vaccine was given at least 14 days prior to specimen collection.
[2] All respiratory specimens submitted through the DoDGRS program were tested regardless of patient's ILI status. ILI determination was made via patient questionnaire. Those marked as unknown are assumed to have (1) met the ILI case definition or (2) be physician determined ILI; however there was not enough information on the questionnaire to make this determination.

VE analysis. An OR greater than one favors the egg-derived vaccine, while an OR less than one favors the cell-derived vaccine. An OR equivalent to one or with the 95% CIs including one indicate there is no difference between the two vaccine types. The only analyses that contained statistically significant results were for the influenza A(H1N1)pdm09 subtype in all dependents [2.0 (1.1, 3.6)] and children [2.9 (1.3, 6.3)]. Influenza A(H1N1)pdm09 was not the predominant subtype for the season, which led to wide CIs; however, the results were statistically significant. In this analysis, influenza A(H1N1)pdm09 showed better protection by the egg-derived vaccine and, although not statistically significant, influenza A(H3N2) suggests better protection from the cell-derived vaccine (Fig. 2, Supplemental Table 3). Supplemental Table 4 displays the group sample size by each influenza subtype, vaccine type, and population category.

Due to the differences in seasonality between the US and Europe, a sensitivity analysis was conducted to verify any statistical differences among specimens tested by USAFSAM and LRMC. In the US, influenza A(H3N2) was the predominant influenza subtype for the 2017–2018 season until week 4 when influenza B began to increase and outcompeted A(H3N2). In Europe, influenza B was the predominant type until week 11 when influenza A(H3N2) increased and was more predominant. In both regions, there were low levels of influenza A(H1N1)pdm09 circulating. When the analysis was performed on specimens processed by only USAFSAM, the results were similar to the combined analysis. However, LRMC results varied due to limited specimen submissions, resulting in statistically insignificant results with wide CIs.

To assess whether bias was introduced by using subjects outside of peak influenza season, a sensitivity analysis was performed and included specimens collected during weeks 50–13 (10 December 2017–31 March 2018). This reduced the number of cases from 1757 to 1648 and controls from 2280 to 1760 for a total sample size of 3408. The vaccination rate of the cases and controls remained relatively stable at 31% and 48%, respectively. Results from the sensitivity analysis were similar to main findings and varied by <3% for most of the cell-derived VE and egg-derived VE. Notable differences occurred in the egg-derived VE for influenza A(H3N2) in adults (increased 9.6%) and cell-derived VE of influenza B in all dependents (decreased 4.9%) The relative VE analyses were similar to the main findings and varied by <0.1.

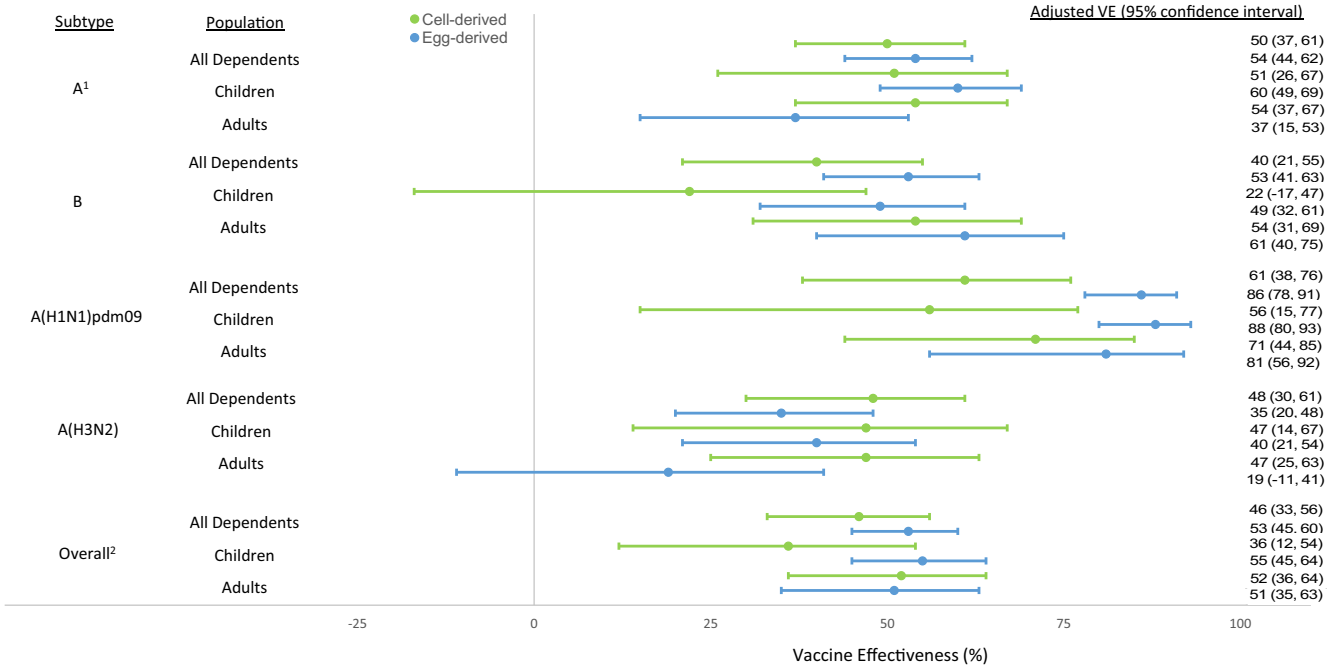

Fig. 1. 2017–2018 Adjusted vaccine effectiveness: Cell-derived vaccine vs unvaccinated and egg-derived vaccine vs unvaccinated (stratified by influenza subtype and beneficiary group). Multivariable logistic regression was used to calculate the odds ratio (OR) using the backward elimination method in SAS version 9.4. Vaccine effectiveness was calculated by $(1 - \text{OR}) \times 100$. Explanatory variables used in the model were time period (based on specimen collection date), age group (6 months - 8 years, 9–17, 18–49, 50–64, 65 and over), and location (Eastern US, Western US, OCONUS). [1]A includes all influenza A specimens (A/unsubtyped, A(H1N1)pdm09, A(H3N2)). [2]Overall includes all influenza types and subtypes (A/unsubtyped, A(H1N1)pdm09, A(H3N2), B).

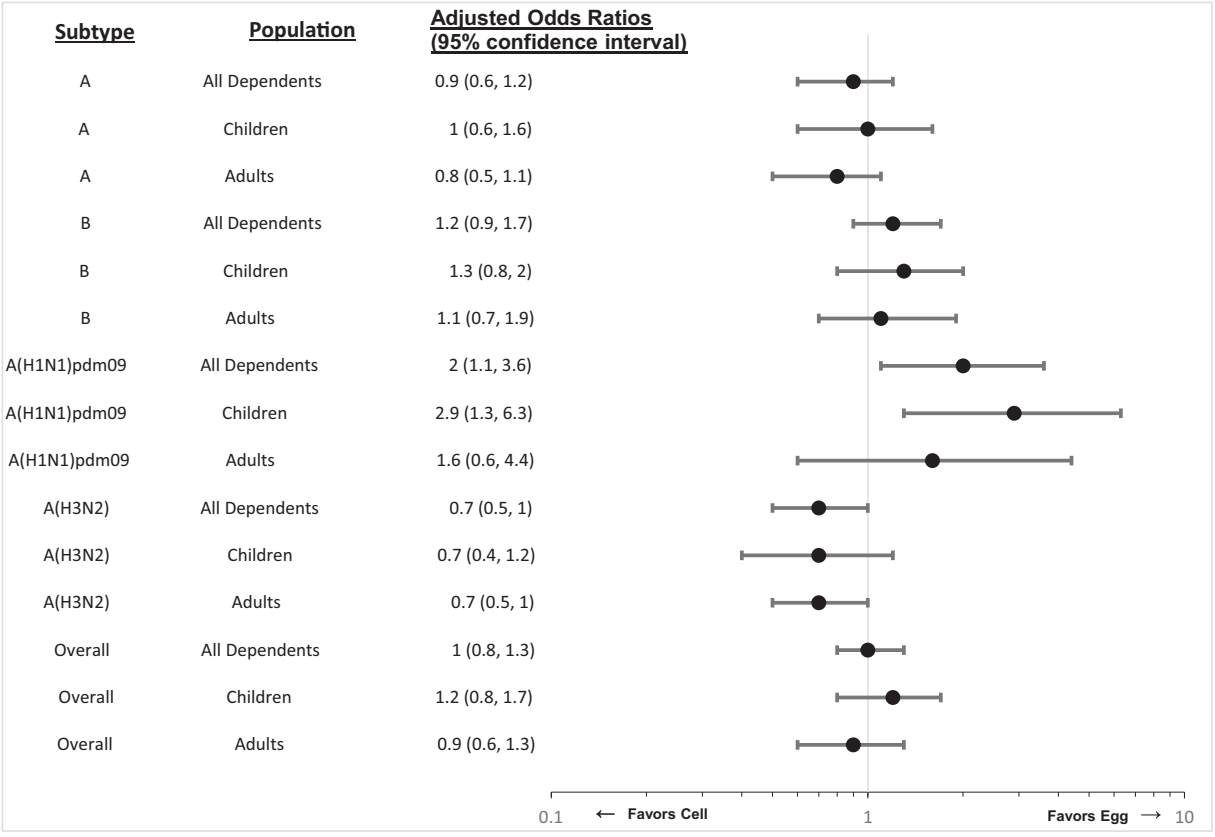

Fig. 2. 2017–2018 Relative vaccine effectiveness: Cell-derived vaccine compared to egg-derived vaccine (Stratified by subtype and beneficiary group). Multivariable logistic regression was used to calculate the odds ratio (OR) using the backward elimination method in SAS version 9.4. Explanatory variables used in the model were time period (based on specimen collection date), age group (6 months - 8 years, 9–17, 18–49, 50–64, 65 and over), and location (Eastern US, Western US, Outside Continental US). Odds ratio <1 favors cell-derived vaccine and odds ratio >1 favors egg-derived vaccine. Subtype A includes all influenza A specimens (A/unsubtyped, A(H1N1)pdm09, A(H3N2)). Overall includes all influenza types and subtypes (A/unsubtyped, A(H1N1)pdm09, A(H3N2), B)

4. Discussion

To our knowledge, this study was the first VE analysis in the DoD to compare the cell-derived vaccine against the egg-derived vaccine among DoD beneficiaries. During influenza A(H3N2) predominant seasons, low VE is often observed which could be a result of repeat vaccinations, host factors, antigenic mismatch due to incorrect strain selection (antigenic drift), or egg-derived mutations during vaccine production [8]. In a blind placebo controlled study by Frey et al. (2010), both cell-derived and egg-derived vaccines performed similarly during the 2007–2008 season against all subtypes, A(H1N1), and B [9]. There was a remarkable decline in VE for the egg-derived vaccine when looking at influenza A(H3N2); however, due to a low attack rate it did not gain statistical significance [9]. Our results were similar to other studies in regards to the influenza A(H3N2) component having lower VE with the egg-derived vaccine compared to the cell-derived vaccine.

There are many advantages of the cell-derived vaccine. The cell stock can be stored frozen and generated quickly as needed and microbial or chemical contamination is reduced due to the closed system of vaccine production [9]. The disadvantages include cost to the consumer (approximately 40% more expensive than egg-derived vaccine), infrastructure does not currently exist to create an adequate supply of cell-derived vaccines to meet current market demands, and mutations could develop in the HA and NA genetic segments from the serial passaging in cell culture (MDCK) [6].

The advantages to the egg-derived vaccine are the low cost that allow all populations to receive the vaccine globally and the infrastructure for production has been used for years [6]. Disadvantages have been seen over the years in the egg passage, especially if a mutation is located near the HA receptor-binding site which negatively effects vaccine antigenicity, immunogenicity, and efficacy [8]. Better vaccine production methods are needed considering the limited supply of eggs and the slow production of vaccine.

This study had several limitations, including the differences in how the vaccination data was obtained. Lack of vaccination was primarily inferred from the self-reported questionnaire which could result in recall bias. Receipt of vaccination originated from an immunization registry (AFCITA), where occasional documentation errors have previously been observed and also may not be complete for DoD dependents outside of the AF. The self-reported questionnaire did not contain enough detail (vaccine type) to use for receipt of vaccination, therefore those individuals were excluded from the analysis if not captured through AFCITA. The distribution of the vaccine and vaccine type was not randomized and was distributed based on product availability and combatant commands. Children were restricted to what types of vaccines were available for their age group. Due to a limited supply of vaccine, the DoD asked adults and children $\geq$9 years of age to receive the Flucelvax (cell-derived) vaccine, if available, in order to conserve the FluLaval and Fluarix (egg-derived) for those younger than 4 years of age. The analyses were performed for one influenza season which limited interpretation of prior and future seasons, subtypes, and overall vaccine effectiveness for each vaccine type. Data on comorbidities and health status was not available, therefore these variables could not be assessed for confounding. Individuals with comorbidities or who are healthier are more likely to be vaccinated, which could affect point estimates. Those with comorbidities are more likely to underestimate VE, while those who are healthier are more likely to overestimate VE [10].

The study also had several strengths. Of the 3.49 million vaccines procured by the DoD, approximately 57% were cell-derived which allowed comparison with egg-derived vaccines (Table 1). The 2017–2018 season had high influenza activity allowing a larger than normal number of specimens available for testing and analysis. Multiple methods were used to collect vaccine data allowing for a more diverse availability of vaccination information. Testing was performed primarily using a combination of either RT-PCR/viral culture or RT-PCR only minimizing the potential for false negative results which can occur through the use of viral culture or rapid antigen tests. The test-negative design is another strength of this study as it is less susceptible to bias due to misclassification of infection, as it excludes persons with influenza who do not seek medical care, and to confounding by health care-seeking behavior as compared to the traditional cohort or case-control design [11].

In order to better evaluate the differences between cell-derived and egg-derived vaccines, more studies are needed; however, they may be limited within the DoD population, as cell-derived vaccines were not purchased in previous seasons or for the 2018–2019 season. Future studies should focus on specific subtypes and span multiple seasons. When comparing cell-derived vaccines prior to 1 September 2016 there may be egg adapted changes due to the CVV being grown in egg. The current season's Flucelvax vaccine is the first vaccine to be produced from a CVV solely from a cell-derived method [12]. This should be considered when making comparisons prior to the 2017–2018 season.

Author contributions

Laurie DeMarcus designed the study, performed data cleaning and analysis, interpretation of the results, and drafted the manuscript. Lisa Shoubaki conducted the literature review, assisted with interpretation of the results, and drafted the manuscript. Susan Federinko performed critical revision of the article and provided program and study oversight. All authors attest they meet the ICMJE criteria for authorship.

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Declaration of Competing Interest

The authors have no conflicts of interest to report.

Disclaimer

The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Air Force, Department of Defense, or the US Government.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.06.004.

References

[1] Rajão DS, Pérez DR. Universal vaccines and vaccine platforms to protect against influenza viruses in humans and agriculture. Front Microbiol 2018;9:123. https://doi.org/10.3389/fmicb.2018.00123.

[2] Shoubaki L, Eick-Cost A, Hawksworth A, Hu Z, Lynch L, Myers C, et al. Brief report: department of defense midseason vaccine effectiveness estimates for the 2017-2018 influenza season. Med Surveill Monthly Rep 2018;25(6):26–8.

[3] Flannery B, Chung JR, Belongia EA, McLean HQ, Gaglani M, Murthy K, et al. Interim estimates of 2017–18 seasonal influenza vaccine effectiveness — United States, February 2018. MMWR Morb Mortal Wkly Rep 2018;67:180–5., https://doi.org/10.15585/mmwr.mm6706a2.

[4] Paules C, Sullivan S, Subbarao K, Fauci A. Chasing seasonal influenza — the need for a universal influenza vaccine | NEJM. [online]. New Engl J Med 2018.

[5] Wu N, Zost S, Thompson A, Oyen D, Nycholat C, McBride R, et al. A structural explanation for the low effectiveness of the seasonal influenza H3N2 vaccine. PLOS Pathogens 2017;13(10):e1006682. https://doi.org/10.1371/journal.ppat.1006682.

[6] Harding AT, Heaton NS. Efforts to improve the seasonal influenza vaccine. Vaccines 2018;6(19):1–12. https://doi.org/10.3390/vaccines6020019.

[7] Department of the Air Force. Air Force 2017-2018 Seasonal Influenza Vaccination Program Implementation Plan; 2017. Available at: https://health.mil/Reference-Center/Policies/2017/08/23/Air-Force-2017-2018-Seasonal-Influenza-Vaccination-Program-Implementation-Plan [accessed 2 July, 2018].

[8] Skowronski DM, Janjua NZ, Serres GD, Sabaidue S, Eshaghi A, Dickinson J, et al. Low 2012–13 influenza vaccine effectiveness associated with mutation in the egg-adapted H3N2 vaccine strain not antigenic drift in circulating viruses. PLoS One 2014;9(3). https://doi.org/10.1371/journal.pone.0092153.

[9] Frey S, Vesikari T, Szymczakiewicz-Multanowska A, Lattanzi M, Izu A, Groth N, et al. Clinical efficacy of cell culture-derived and egg-derived inactivated subunit influenza vaccines in healthy adults. Clin Infect Dis 2010;51(9):997–1004. https://doi.org/10.1086/656578.

[10] Remschmidt C, Wichmann O, Harder T. Frequency and impact of confounding by indication and health vaccinee bias in observational studies assessing influenza vaccine effectiveness: a systematic review. BMC Infect Dis 2015;15(429). https://doi.org/10.1186/s12879-015-1154-y.

[11] Jackson ML, Nelson JC. The test-negative design for estimating influenza vaccine effectiveness. Vaccine 2013;31(17):2165–8. https://doi.org/10.1016/j.vaccine.2013.02.053.

[12] Cell-Based Flu Vaccines | Seasonal Influenza (Flu) | CDC; (2016, November 7). Available at https://www.cdc.gov/flu/protect/vaccine/cell-based.htm.\