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Article

Influenza vaccine effectiveness by age for Influenza A/B viruses between 2011-2020

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SUMMARY

Understanding whether influenza vaccine effectiveness (VE) varies by age is crucial to determine which populations need refinements in vaccination strategy or additional measures to reduce influenza rates, hospitalizations, and deaths. Our objective was to analyze the mean VE for different strains of influenza across five age groups: 6 months–8 years, 9–17 years, 18–49 years, 50–64 years, and 65+ years old. We used VE data for Influenza A, H3N2, and H1N1 strains, and Influenza B vaccines from the Centers for Disease Control and Prevention (CDC), collected between 2011–2020. We compared VE rates across different years, strains, and age groups. Overall, VE varied significantly by year, strain, and age group ($p < 0.05$, one-way ANOVA). The youngest age group (6 months–8 years) had a significantly higher VE than both the 18–49 years old and 65 years old or greater age groups ($p<0.05$, one-way ANOVA). Future vaccine development should be tailored to these two distinct populations to ensure adequate protection against influenza.

INTRODUCTION

Each year, public health authorities mount vaccination campaigns to combat the significant individual and public health impacts of illness due to seasonal influenza, yet even among the vaccinated, protection against influenza is not equal (1-3). Understanding how well different age groups respond to vaccination may identify which groups need a more effective alternative to optimize protection against influenza.

Influenza is a contagious and endemic respiratory virus that infects the nose, throat, and lungs (4). It spreads primarily among people in semi-enclosed or crowded environments during the winter season, causing a respiratory illness commonly known as the flu (5). There are four main influenza strains (A, B, C and D) that differ in their types of surface protein, which are vital in immune cell recognition (4). Among humans, the A and B strains are mainly responsible for causing seasonal influenza, with influenza A being more common than influenza B (4). Influenza A is categorized into subtypes, such as H1N1 and H3N2, depending on the type of two antigens: hemagglutinin (H) and neuraminidase (N) (4). These surface proteins facilitate viral attachment, entry, and exit into host cells, and can trigger an immune response by the host (4,6). Similarly, influenza B is categorized into two main lineages known as B/Yamagata and B/Victoria (4).

Children under five years of age, individuals with medical conditions, and people aged 65 years and older have the highest risk of serious illness, hospitalization, and death from influenza (7). Health professionals recommend the seasonal flu vaccine for most individuals over six months of age (8). A vaccine cannot cause the flu in an individual, however it enables the person's immune system to produce protective antibodies (9). There are two main types of influenza vaccines that currently exist: inactivated influenza vaccines (IIV) and live attenuated influenza vaccines (LAIV) (8). Inactivate vaccines use a dead version of the virus whereas live vaccines use a weakened virus to generate an immune response (9). Although the immune system response differs somewhat across each type of vaccine, both stimulate antibody creation (6). However, LAIV has a slim chance of replicating within the body and therefore is not recommended in immunocompromised individuals (9). Immune responses are not as long lasting with IIV vaccines, and multiple doses may be needed for full immunity. IIV are typically used for those that are aged 6 months and older including pregnant women, while the LAIV vaccine may only be used for those between the ages of 2 to 49 years without underlying medical conditions to ensure tolerability (6). Yearly vaccination for influenza is recommended because the strain of influenza changes each season due to antigenic drift, the ongoing genetic variation in the surface proteins of the virus (4,6). Therefore, even if an individual has had previous vaccination or exposure, they can still be at risk in the following season (1,2). Thus, new vaccines should be created to best match the most prevalent strains of influenza that year. The World Health Organization (WHO) makes recommendations on the composition of flu vaccines twice a year based on circulating strains in the northern and southern hemispheres (6).

Influenza vaccines can be trivalent or quadrivalent (6). Trivalent vaccines protect only against three strains of the influenza, while the quadrivalent vaccines protect against all four subtypes of influenza A and B. However, vaccine effectiveness (VE) of the trivalent vaccine is similar to the quadrivalent vaccine (7,10). Literature evaluating influenza vaccine presents two common terms for describing their success: VE and vaccine efficacy (11). VE is a measure of how well vaccines work in the real world, whereas vaccine efficacy is measured in a controlled setting, such as in a lab or clinical trial (11). VE determines the relative difference vaccinations have on virus susceptibility and is calculated according to the following equation (12):

$$\frac{(Risk\ among\ unvaccinated\ group - risk\ among\ vaccinated\ group)}{Risk\ among\ unvaccinated\ group}$$

VE is influenced by several factors which include the strain of the virus, age, comorbidities, as well as prior exposure and time of vaccination (3,9,13). Children under 5 years old have similar hospitalization rates to people aged 65–74 years and older, suggesting that VE may vary with age (14). Aside from young children, in general, VE appears to decrease as age increases (3). As individuals age, their immune system goes through immunosenescence, resulting in a decline in function (15). With aging, the immune system is not as responsive to viral or other pathogenic exposures. A study of influenza vaccines in monkeys demonstrated immunosenescence, where monkeys in the old and very old categories had lower antibody response (15). Similarly, a study in humans vaccinated against the influenza virus showed that the number of antibodies were consistently higher in younger people compared to older people (15).

Understanding which age groups respond best over time is important because it allows researchers and clinicians to determine what groups need improvement in VE. We analyzed influenza VE, across all age groups, for both the Influenza A and B viruses between 2011–2020. Based on available prior research, we hypothesized that VE will be highest in the 18–49-year age group and lowest in those over 65 years old. We found VE to be significantly influenced by age, strain, and year. VE was lowest in the 18–49 years old and 65 years old or greater age groups suggesting these groups need additional therapeutic support and preventative measures against influenza spread.

RESULTS

We analyzed VE by virus subtype collected by the CDC from 67,688 individuals across five age groups over nine previous flu seasons (2011-2020, **Table 1**) (16). Between 2011–2020, mean VE against all influenza (A and B) was 47.78±12.81% for children 6 months to 8 years old and 38.78±16.77% for children 9–17 years old, 34.11±15.35% for adults aged 18–49, 38.67±17.81% for adults aged 50–64 years and 31.22±13.20% for those 65 years and older (**Table 2**). During the same timeframe, the mean VE across all age groups varied substantially year to year from 21.8% to 52.2% and the standard deviation ranged from 3.13%–19.01%, representing the variation between age groups (**Figure 1**). Additionally, significant differences were seen in VE which were most prominent between the 6 month-8 year and 18–49-year group ($p < 0.05$, one-way ANOVA, **Figure 2**). We conducted two-way ANOVA tests to account for both age group and strain, which both showed significant differences in VE ($p < 0.05$, two-way ANOVA). Further, the 6 months to 8 years age group had a significantly higher VE than both the 18–49 years old age group and the over 65 age group ($p < 0.05$, Tukey's HSD**) (Figure 2**). Mean VE was significantly different across different strains ($p < 0.05$, one-way ANOVA). There was significantly lower VE of influenza A H3N2 strain compared to influenza A H1N1 strain ($p < 0.05$, Tukey's HSD) (**Figure 3**). In general, influenza vaccines offer little protection to influenza A H3N2 in comparison to other influenza strains, since the H3N2 strain is not as common in humans (17).

There was a high level of variance in VE based on age and year with significant differences in at least two groups ($p < 0.05$, two-way ANOVA). The mean value of VE was significantly different between the 6 months–8 years age group and 18–49 years age group ($p < 0.05$, Tukey's HSD). There was also a significant difference between the 6 months–8 year age group and 50–64 year old age group when accounting for yearly differences ($p < 0.05$, Tukey's HSD). Finally, there was also a significant difference between those 65 years and older versus 6 months to 8 years age groups ($p < 0.05$, Tukey's HSD). Variance in VE is most accounted for when the effects of age group, year and strain are considered. Further, differences in VE across age groups are more apparent when controlling for annual and strain-dependent variation.

DISCUSSION

In this study, we showed that VE for influenza varies from season to season ranging from 21.8%–52.2% between 2011–2020, but in most years was on average less than 50% effective. We saw differences in VE according to age, including a significant difference with higher VE among the youngest group (6 months–8 years) versus adults (18–49 years old) as well as between the oldest (65+ years) and the youngest age group.

Other studies have shown different results with no pattern of decreasing VE with age across five seasons (18). In a previous study, VE was said to be no different in older adult

	2011-12	2012-13	2013-14	2014-15	2015-16	2016-17	2017-18	2018-19	2019-20	TOTAL
Gender										
Male	2417	2654	2367	3923	2833	2993	3453	4018	3675	**28333**
Female	2354	3798	3632	5288	4046	4090	4983	5994	5169	**39354**
TOTAL	**4771**	**6452**	**5999**	**9211**	**6879**	**7083**	**8436**	**10012**	**8845**	**67688**
Age group										
6 mo – 8 yrs	1490	1509	1125	2419	1526	1519	1109	2428	2011	**15136**
9 – 17 yrs	666	981	625	1342	858	1011	1802	1261	1193	**9739**
18 – 49 yrs	1549	2267	2168	2848	2456	2165	2859	3256	3258	**22826**
50 –64 yrs	682	1040	1096	1496	1201	1362	1508	1766	1348	**11499**
65+ yrs	384	655	623	1206	383	1026	1158	1301	1035	**7771**
TOTAL	**4771**	**6452**	**5999**	**9211**	**6879**	**7083**	**8436**	**10012**	**8845**	**67688**

Table 1. Number of both vaccinated and unvaccinated individuals tested for influenza from 2011–2020. Individuals between the ages of 6 months and 65+ years were tested. Data is grouped by age and gender across seasons. Data for table was collected by the CDC (16). Abbreviations: mo = months, yrs = years.

	Vaccine Effectiveness (%)										
Age Group	2011-12	2012-13	2013-14	2014-15	2015-16	2016-17	2017-18	2018-19	2019-20	**MEAN**	**SD**
6 mo – 8 yrs	45	57	45	25	51	57	68	48	34	47.778	12.814
9-17 yrs	58	39	53	25	59	36	32	7	40	38.778	16.717
18-49 yrs	44	39	54	7	52	19	33	25	34	34.111	15.350
50-64 yrs	54	65	59	20	26	40	30	14	40	38.667	17.812
65+ years	43	26	50	32	42	20	17	12	39	31.222	13.198
MEAN Across All Age Groups	48.8	45.2	52.2	21.8	46	34.4	36	21.2	37.4	-	-
SD	6.760	15.627	5.167	9.311	12.708	15.726	19.013	16.362	3.130	-	-

Table 2. Influenza vaccine effectiveness against influenza A or B viruses for each age group across seasons. Mean and standard deviation are also indicated for each year and age group (16). Abbreviations: mo = months, yrs = years.

age groupings (65–74, 75+, or 65+ years) when compared with younger adults (18). More limited data was available for comparison for Influenza A (H3N2), Influenza A (H1N1) subtypes and influenza B viruses, however, there was no significant difference in VE between the older age groups and adults aged 18–49 years (18). In contrast to our study, which looked at nine flu seasons and included greater than 65,000 individuals both children and adults, the study by Russell et al. examined only five seasons and included 20,907 outpatients aged 18 years or older (19). Differences in the participants sampled, varying influenza strains and external factos could account for observed differences. Our results are consistent with studies that show decreased immune response among older adults (15). In a meta-analysis that analyzed 9 studies of VE, data on VE in those 65 years old or greater is lacking, as there were only two studies in adults of that age (20). Given the limited, and conflicting information about VE in those 65 years old or greater, more information is needed to better understand how well influenza vaccines work in the elderly. Further, more information is needed to elaborate on why the 18–49 years age group showed lower VE than the youngest age group. Perhaps, since this group has greater natural immunity to the virus, vaccines only pose a modest benefit in viral recognition and elimination (21).

Our study had several limitations. The significant yearly variation in influenza strains and VE makes it difficult to isolate and interpret findings regarding VE by age group (**Figure 1**). For any given year, the spread of influenza among different age groups may vary (22). Further, variability in numbers of individuals vaccinated can also skew the findings. For instance, the lower VE during the 2014–2015 influenza season may have been caused by a lack of participants that were vaccinated. Alternatively, the 18–49 years old age group had an extremely low VE rate in this year, making it a potential outlier. A very low vaccine uptake is likely to result in lower VE since the greater number of unvaccinated individuals with the disease will result in an increased disease risk of vaccinated individuals (20). Lastly, VE is based on influenza infection rates, not hospitalization rates, therefore comparing how vaccines lower hospitalization attributable to influenza is not captured. A future direction is to investigate the protection of vaccines against hospitalizations due to the influenza virus. This analysis will help illuminate the social and economic impacts of influenza that could potentially be averted with vaccination.

We observed that VE varies substantially year-to-year and is limited in older adults (65+ years). Variability in VE year to year may be due to a mismatch in the antigens included in the

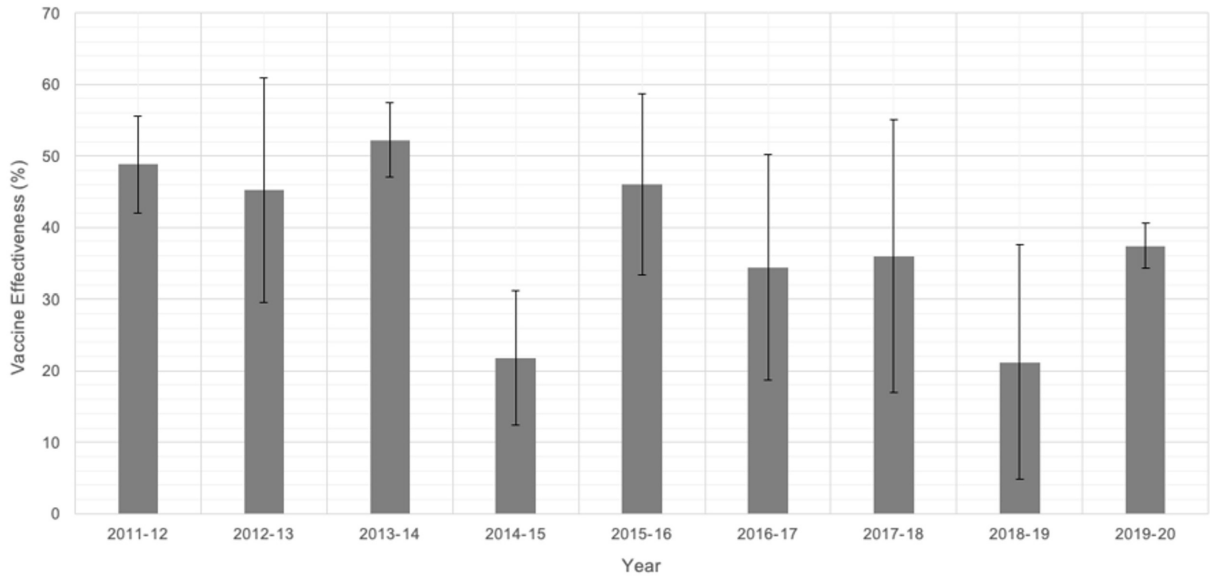

Figure 1. Mean Vaccine Effectiveness Varied across 9 seasons from 2011 to 2020. VE across all age groups shown by year from 2011 to 2020. VE was averaged across each age group and strain. Data shown as mean ± standard deviation.

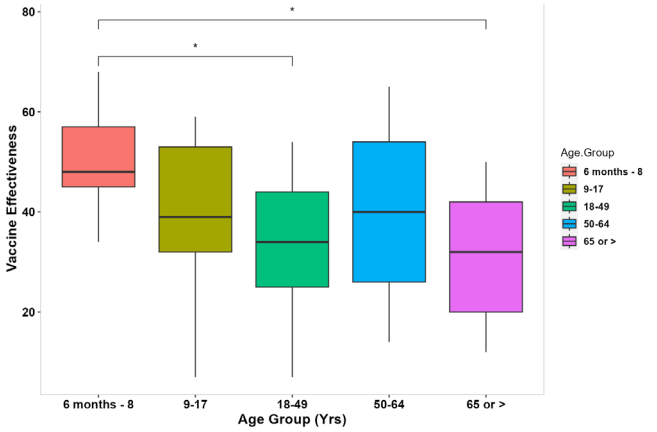

Figure 2. Vaccine effectiveness across age groups (2011-2020). This box plot shows the range as well as upper, middle, and lower quartile of mean VE from each influenza season in 2011-2020 by each age group. A two-way ANOVA with a post-hoc Tukey-HSD was conducted. *p<0.05.

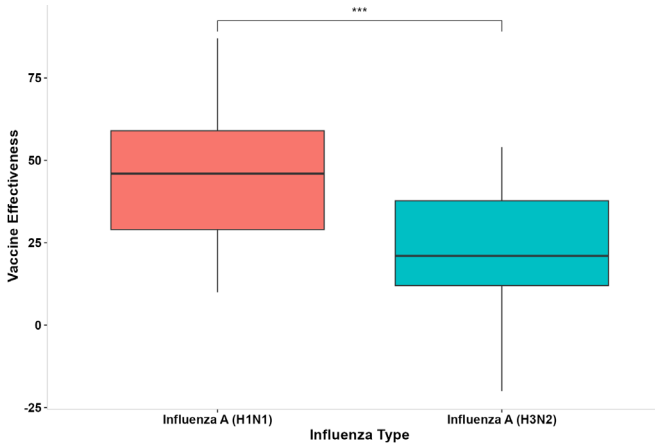

Figure 3. Vaccine effectiveness by influenza strain (2011-2020). This box plot shows the range as well as upper, middle, and lower quartile of mean VE from each influenza season in 2011–2020 against influenza dependent on influenza strain. A one-way ANOVA with a post-hoc Tukey-HSD showed significant differences across strains (***p < 0.001).

vaccines versus the antigens on the circulating strain of flu in each season (9). Identifying populations in which VE is not optimal may allow health authorities and health care providers to recommend other strategies on top of vaccines to protect against influenza. For instance, with the use of masks during the pandemic, the influenza case rate for 2020–2021 decreased to the lowest numbers in six consecutive seasons (23). Therefore, masks may be an easy, viable method of improving protection against the spread of influenza, particularly for age groups in which VE is lower. Another therapy for more severe influenza cases may include monoclonal antibody treatments; by attaching to certain locations on the virus' spike protein, artificial antibodies enter the body to replicate the body's natural immune system, hindering the virus from reaching cells and proliferating (24). Vaccines on their own should not be strictly relied upon to mitigate the influenza burden, especially for populations with limited rates of vaccination or insufficient VE. Future development of influenza vaccines and other preventative measures should be tailored to children and older adult populations as they share the greatest risk for influenza and have suboptimal VE.

MATERIALS AND METHODS

We used data summarized by the CDC website to examine VE (16). The CDC data included information about the estimated seasonal VE and 95% confidence interval [95%CI]) by age group (6 months to 8 years, 9–17 years, 18–49 years, 50–64 years, 65+ years) and virus subtype for both vaccinated and unvaccinated individuals. To calculate VE, the risk of influenza in both unvaccinated and vaccinated individuals was determined and compared. The CDC VE estimates were calculated from two general types of studies, randomized controlled trials and observational studies (25-33). We calculated the mean VE for each year between 2011–2020 by age group. We then did one-way and two-way analysis of variance (ANOVA) using the statistical program R to compare VE-Year, VE-Age Group, VE-age-strain, VE-Age-Year and VE-age-year-strain. We checked for any significant p-values (< 0.05) and performed Tukey's HSD test to find post-hoc differences in means.

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