Analyzing Influenza Vaccine Effectiveness By Age for Influenza A/B Viruses Between 2011-2020

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ABSTRACT

Analyzing influenza vaccine effectiveness for various age groups is crucial to determine which populations might need refinements in vaccination strategy or additional measures to reduce influenza rates and in turn, hospitalization and deaths. The objective of this study was to understand the mean vaccine effectiveness for different strains of influenza across five age groups, 6 months-8 years, 9-17 years, 18-49 years, 50-64 years, and greater than 65 years old. The vaccine effectiveness for Influenza A, H3N2 and H1N1 strains, and Influenza B vaccines were compared between different age groups. Then, a one-way ANOVA test was used to analyze the vaccine effectiveness data collected from 67,688 individuals between 2011 to 2020. Tukey's Honest Significant Difference (HSD) test was performed for post-hoc differences in means. The results show that there were no statistically significant differences in vaccine effectiveness between the older age groups and adults aged 18–49 years. The ANOVA test and Tukey's HSD tests show a statistically significant difference between the youngest age group (6 months-8 years) and adults from age 18-49 years. Similarly, there is a significant difference between the vaccine effectiveness from the oldest age group (65+ years) and the youngest. Ultimately, the results demonstrate that vaccine effectiveness varies significantly between each year and is limited in both young children and older adults. Future therapeutic development should be tailored to these distinct populations to ensure adequate protection against influenza.

Key Words: Vaccine effectiveness, Influenza H3N2/H1N1, Age

INTRODUCTION

Influenza is a contagious and endemic respiratory illness that infects the nose, throat, and lungs. It spreads primarily among people in semi-enclosed or crowded environments during the winter season. There are four main influenza strains: A, B, C and D that each differ in their types of surface protein[1]. Among humans, influenza is mainly caused by the A and B strains. Generally, influenza A is more common than influenza B, as it can infect both humans and animals whereas influenza B only affects humans. Influenza A is categorized into subtypes depending on the amount of two antigens, hemagglutinin, and neuraminidase, proteins on the surface of each strain that can trigger an immune response in the body. H1N1 and H3N2 subtypes of influenza A. Similarly, influenza B is categorized into two main lineages known as B/Yamagata and B/Victoria.

Children under the age of 5 years, individuals with medical conditions, and people aged 65 years and older have the highest risk of serious illness, hospitalization, and death from influenza[2]. However, the seasonal flu vaccine is recommended for everyone. A vaccine can contain either an attenuated virus or an inactive part of a specific viral antigen that triggers an immune response within the body; the vaccine cannot cause the flu in an individual, however it enables the person's immune system to produce protective antibodies[3]. There are two types of influenza vaccines that currently exist: inactivated influenza vaccines (IIV) as well as live influenza vaccines (LAIV)[4]. The immune system response is similar in both cases, as they stimulate roughly the same antibody creation, however, LAIV has a slim chance of replicating within the body while the IIV cannot[5]. Immunity is not as long lasting with IIV vaccines and multiple doses may be needed for full immunity. IIV are typically used in 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 [4]. Yearly vaccination for influenza is recommended because the strain of influenza changes each season so even if an individual has had previous vaccination or exposure, they could still be at risk.

Influenza vaccines can be trivalent or quadrivalent. Trivalent vaccines protect only against three strains of the influenza while the quadrivalent vaccines protect against all four strains. However, when comparing vaccine effectiveness against only influenza B strains, the trivalent vaccine has a slightly higher overall effectiveness than the quadrivalent. Literature evaluating influenza vaccine presents two common terms for describing their success: vaccine effectiveness and vaccine efficacy. Vaccine effectiveness (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[6]. VE determines the relative difference vaccinations have on virus susceptibility and is calculated according to the following equation[7]:

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

VE is influenced by several factors which include the strain of the virus, age, comorbidities, as well as prior exposure and time of vaccination. Children under 5 years have similar hospitalization rates as people aged 65 years and older suggesting that VE may vary with age. Aside from young children, in general, VE appears to decrease as age increases[8]. As individuals age, their immune system goes through immunesenescence meaning that there is a decline in function[9]. With aging, the immune system is not as responsive to viral or other pathogenic exposures. A study of influenza vaccines in monkeys demonstrated immune senescence, where monkeys in the old and very old categories had lower antibody responses[9].

Similarly, a study in humans vaccinated against the influenza virus showed that the number of antibodies were consistently higher in younger people compared to those who were older[9]. Understanding which age groups respond best over time is important because it allows researchers and clinicians to determine what groups need improvement in vaccine effectiveness. The objective of this project was to analyze the influenza vaccine effectiveness, across all age groups, for both the Influenza A and B viruses between 2011-2020. Based on prior research, we hypothesized that vaccine effectiveness (VE) will be highest in the 18-49 year age group and lowest in those over 65 years old.

METHODS

We used data summarized by the Centers for Disease Control (CDC) and Prevention website[10] to examine VE. The CDC data includes 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. The CDC VE estimates were calculated from two general types of studies, randomized controlled trials and observational studies. Table 2 summarizes VE of all influenza A or B vaccine by age. We calculated the mean VE for each year between 2011-2020 by age group. We then did an 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 the Tukey Honest Significant Difference (HSD) test to find post-hoc differences in means.

RESULTS

We summarized the CDC estimates of seasonal influenza vaccine effectiveness from 9 previous seasons (2011-2020), including estimated VE by age group and virus subtype. Information on VE was collected by the CDC from 67,688 individuals across 5 age groups.

Table 1 summarizes the demographic characteristics of all evaluated individuals. Mean VE against influenza A or B viruses each year is broken down by age group (Table 2). Between 2011-2020, mean VE (standard deviation) against all influenza (A and B) was 47.778% (SD 12.814) for children 6 months to 8 years old and 38.778% (SD 16.77) for children 9-17 years old, 34.111% (SD 15.350) for adults aged 18-49, 38.667% (SD 17.812) for adults age 50-64years and 31.222%(SD13.198) for those 65 years and older. During the same timeframe, the mean VE across all age groups varied substantially year to year from 21.8% to 52.2% (Figure 1) and within each year, the standard deviation ranged from 3.13%-19.013%, representing the variation between age groups.

A one-way ANOVA was performed to compare the effect of age group on VE. The one-way ANOVA revealed that there was a statistically significant difference of age between at least two groups ($F(4, 90\ df) = [3.001]$, $p = 0.0225$). Tukey's HSD Test for multiple comparisons found that the mean value of VE was significantly different between the 6 months-8 year age group and the 18-49 year old age group ($p = 0.0426$, 95% C.I. = 0.3695, 33.74). There was also a statistically significant difference between those 65 years and older versus the 6 months to 8 year age group ($p=0.0258$), 95% C.I. = -34.84, -1.474). Interestingly, in both cases the vaccine was shown to be significantly more effective in the 18-49 year or 65 year and older groups in comparison to the 6 months to 8 years group.

A two-way ANOVA was then performed to compare the effect of age groups and influenza strains on VE. The two-way ANOVA showed that there was a statistically significant difference in VE between at least two groups ($F(4, 88\ df) = [3.64]$, $p = 0.0086$). Tukey's HSD Test for multiple comparisons found that the mean value of VE was significantly different between the 6 months-8 year age group and 18-49 year old age group ($p=0.0194$, 95% C.I. =1.897, 32.21)

[Figure 2a]. Similarly, there was also a statistically significant difference between those 65 years and older versus 6 months to 8 years (p=0.0106), 95% C.I. = -33.31, -3.002) [Figure 2a]. Tukey's HSD Test also demonstrated the mean VE was significantly different between the influenza A H3N2 strain compared to all influenza strains (p=0.005, 95% C.I. =-22.60, -3.28), as well as between the influenza A H3N2 strain compared to influenza A H1N1 strain (p<0.001, 95% C.I. =-31.15, -9.50) [Figure 2b].

A two-way ANOVA was also performed to compare the effect of age groups and year (season) on VE. The two-way ANOVA showed that there was a statistically significant difference in VE between at least two groups (F(4, 82 df) = [4.66], p <0.001). Tukey's HSD Test for multiple comparisons found that the mean value of VE was a statistically significant difference between the 6 months-8 year age group and 18-49 year old age group (p=0.006, 95% C.I. =3.64, 30.46). Similarly, there was significantly different between the 6 months-8 year age group and 50-64 year old age group (p=0.021, 95% C.I. =1.59, 28.41). Finally, there was also a statistically significant difference between those 65 years and older versus 6 months to 8 years age groups (p=0.003), 95% C.I. = -31.57, -4.75).

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. The one-way ANOVA suggests differences in VE according to age and Tukey's test showed a statistically significant different between the youngest group (6 months-8 years) versus adults 18-49years and similarly between the oldest (65+ years) and the youngest age group. Other studies that have shown different results with no pattern of decreasing VE with age across 5 seasons[11]. Vaccine effectiveness was said to be no different in older adult age groupings (65–74 years, ≥75 years, or ≥65 years) when compared with younger adults [11]. More limited data was available for comparison for Influenza A(H3N2), Influenza A(H1N1) subtypes and influenza B viruses, but again, overall, there was no statistically significant differences in VE between the older age groups and adults aged 18–49 years[11]. In contrast to our research, which looked at 9 flu seasons and included > 65,000 individuals both children and adults, the study by Russell et al. (2018) examined only 5 seasons and included 20,907 outpatients aged ≥18 years. The differences in the populations and time could account for observed differences. Our results are consistent with studies that show decreased immune response among older adults[9]. In a meta-analysis that analyzed 9 studies of VE, data on VE in those 65+ years is lacking, as there were only two studies in adults of that age[12]. Given the limited, and conflicting information about VE in those 65+ years, 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 18-49year age group showed lower VE. Perhaps, since this group has greater natural immunity to the virus, vaccines only pose a modest benefit in viral recognition and elimination[13].

Identifying populations in which vaccination may not be as effective may also allow health care providers to recommend other strategies to protect against influenza. For instance, with the use of masks during the pandemic, the influenza case rate has decreased from an average of around 38,000 to just slightly higher than 551 this season. Therefore, masks are a viable method of improving protection against the spread of influenza over and above vaccines[14].

Limitations

After analyzing the data shown in Figure 1, the dip caused during the 2014-2015 influenza season may have been caused by either a lack of participants that were vaccinated or as seen in Table 2, the 18-49 year age group had an extremely low vaccine effectiveness rate therefore causing a very distinct outlier in the data figure.

The significant yearly variation in influenza strains and VE, makes it difficult to isolate and interpret findings regarding VE by age group. For any given year, a different age group may be more or less at risk of influenza. VE is based on infection rates of influenza and not hospitalization rates therefore comparing how impact of vaccines on lowering hospitalization rates due to influenza is not captured. Hospitalization due to influenza virus is another important outcome that needs to be analyzed.

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Table 1: Number of individuals tested from 2011-2020 (6 months to 65+ years).

	2011-2012	2012-2013	2013-2014	2014-2015	2015-2016	2016-2017	2017-2018	2018-2019	2019-2020	**TOTAL**
Gender										
Male	2417	2654	2367	3923	2833	2993	3453	4018	3675	**28333**
Females	2354	3798	3632	5288	4046	4090	4983	5994	5169	**39354**
TOTAL	**4771**	**6452**	**5999**	**9211**	**6879**	**7083**	**8436**	**10012**	**8845**	**67688**
Age groups										
6 months- 8 years	1490	1509	1125	2419	1526	1519	1109	2428	2011	**15136**
9 – 17 years	666	981	625	1342	858	1011	1802	1261	1193	**9739**
18- 49 years	1549	2267	2168	2848	2456	2165	2859	3256	3258	**22826**
50-64 years	682	1040	1096	1496	1201	1362	1508	1766	1348	**11499**
65+ years	384	655	623	1206	383	1026	1158	1301	1035	**7771**
TOTAL	**4771**	**6452**	**5999**	**9211**	**6879**	**7083**	**8436**	**10012**	**8845**	**67688**

Table 2: Influenza vaccine effectiveness for all vaccine types, against influenza A or B viruses including mean ± standard deviation (yrs = years).

	Vaccine Effectiveness (%)									
Age Group (yrs)	2011-12	2012-13	2013-14	2014-15	2015-16	2016-17	2017-18	2018-19	2019-20	Mean±SD
6 months - 8	45	57	45	2	51	57	68	48	34	47.8±12.8
9 - 17	58	39	53	25	59	36	32	7	40	38.8±16.7
18 - 49	44	39	54	7	52	19	33	25	34	34.1±15.4
50 - 64	54	65	59	20	26	40	30	14	40	38.7±17.8
≥ 65	43	26	50	32	42	20	17	12	39	31.2±13.2
Mean±SD	48.8±6.8	45.2±15.6	52.2±5.2	21.8±9.3	46±12.7	34.3±15.7	36±19.0	21.2±16.4	37.4±3.1	–

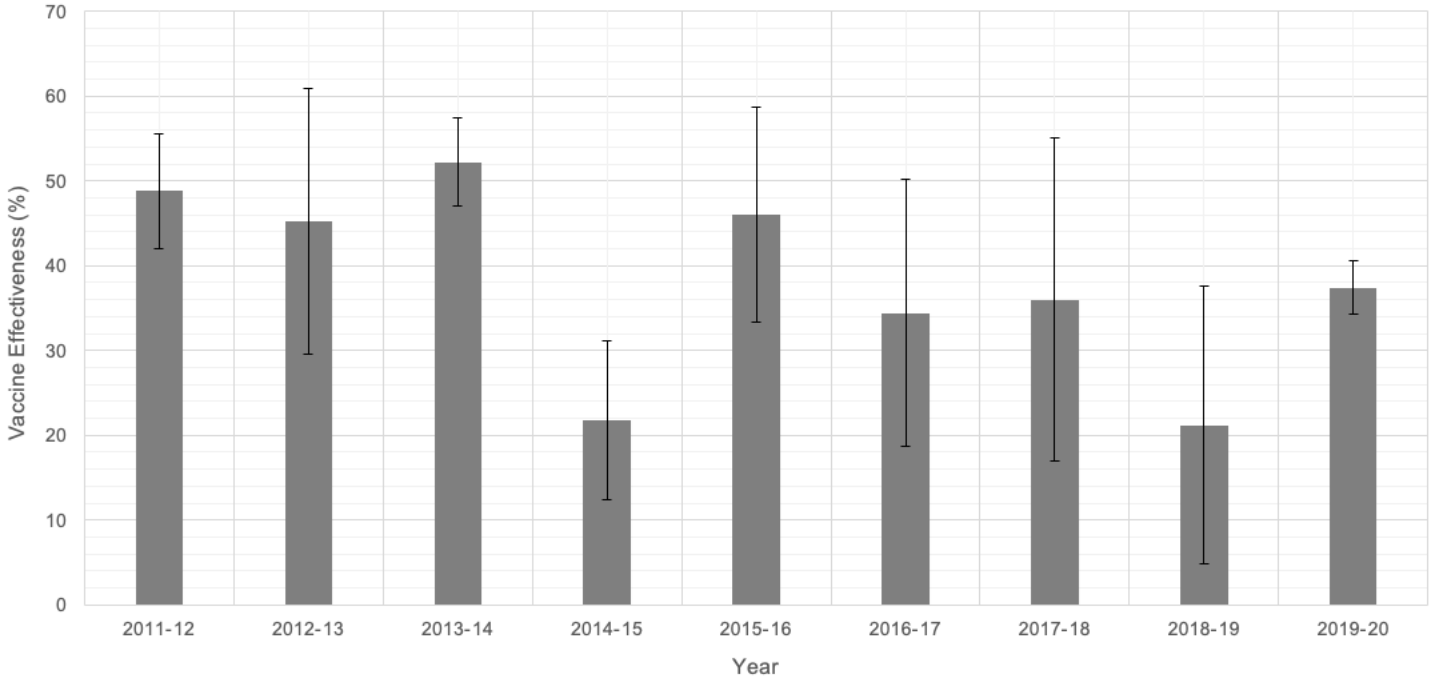

Figure 1: Mean Vaccine Effectiveness from 2011 to 2020.

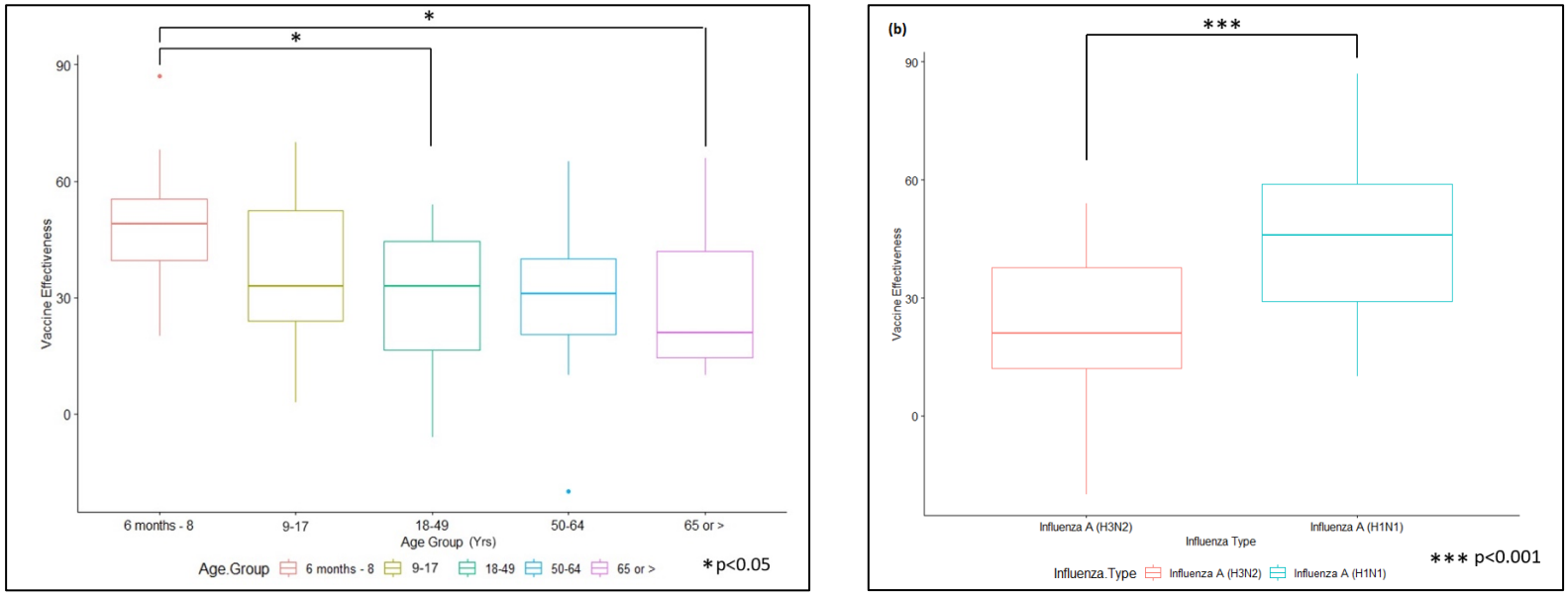

Figure 2 (a) Vaccine effectiveness across age groups. (b) Vaccine effectiveness by influenza strain.

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