

Seasonal Influenza Vaccine Impact on Pandemic H1N1 Vaccine Efficacy

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Background. In 2009, a novel influenza A (pH1N1) was identified, resulting in a pandemic with significant morbidity and mortality. A monovalent pH1N1 vaccine was separately produced in addition to the seasonal trivalent influenza vaccine. Formulation of the seasonal influenza vaccine (injectable trivalent inactivated influenza vaccine [TIV] vs. intranasal live, attenuated influenza vaccine [LAIV]) was postulated to have impacted the efficacy of the pH1N1 vaccination.

Methods. We reviewed electronic health and databases, which included vaccination records, and healthcare encounters for influenza-like illness (ILI), influenza, and pneumonia among US military members. We examined rates by vaccination type to identify factors associated with the risk for study outcomes.

Results. Compared with those receiving the seasonal influenza vaccine alone, subjects receiving the pH1N1 vaccine, either alone (RR, 0.49) or in addition to the seasonal vaccine (RR, 0.51), had an approximately 50% reduction in ILI, 88% reduction in influenza (RR, 0.11 and 0.12, respectively), and 63% reduction in pneumonia (RR, 0.37 and 0.35, respectively). There was no clinically significant difference in ILI, influenza, or pneumonia attack rates among those receiving the pH1N1 vaccine with or without presence of the seasonal vaccine. Similarly, there was no clinically relevant difference in pH1N1 effectiveness between seasonal TIV and LAIV recipients.

Conclusions. During the 2009–2010 pandemic, the pH1N1 vaccination was effective in reducing rates of ILI, influenza, and pneumonia. Administration of the seasonal vaccine should continue without concern of potential interference with a novel pandemic vaccine, though more studies are needed to determine if this is applicable to other influenza seasons.

Keywords. influenza; influenza-like illness; vaccine efficacy; vaccine formulation; pandemic influenza vaccine.

A novel pandemic H1N1 (pH1N1) swine-origin influenza A virus emerged in April 2009, resulting in widespread illness, and high rates of morbidity and mortality [1]. In the United States, there was a clinical attack rate of about 19.9%, an estimated 274 300 hospitalizations, and 12 469 deaths [2]. A high rate of severe disease in children and younger adults, with apparent protection of older age groups, suggested previous exposure and priming to this strain or cross-reactivity from prior swine influenza vaccine [3]. This is in part due to shift and drift of the influenza virus, resulting in new strains to which humans have limited protective immune responses. In general, influenza continues to be a leading cause of illness and is a major public health concern [4]. Although the most effective prevention strategy is vaccination, vaccine efficacy varies markedly from year

to year depending on how well the vaccine matches the circulating strains, vaccine formulation, and other factors [5]. Thus, continued research into preventive strategies is needed to better understand the variables associated with effectiveness. A large segment of the population receives the seasonal influenza vaccination; therefore, its role in the pandemic is clinically relevant.

There were 2 main types of seasonal influenza vaccines licensed in the United States in 2009—the injectable trivalent inactivated influenza vaccine (TIV) and the intranasal live, attenuated influenza vaccine (LAIV) [6–11]. Although other formulations have since been approved by the US Food and Drug Administration (FDA), such as the quadrivalent, intradermal, and high-dose inactivated influenza vaccines, this study was performed when TIV was the only inactivated formulation available. Typically, each type of vaccine contains 3 influenza strains that are chosen annually by influenza experts from the World Health Organization internationally and by the Centers for Disease Control and Prevention (CDC) and FDA Vaccines and Related Biological Products Advisory Committee domestically. One seasonal influenza A (H1), 1A (H3), and 1B strain are selected for inclusion [6]. However, during the 2009–10 season, a novel monovalent 2009 influenza A (pH1N1) vaccine (strain A/California/7/2009(H1N1)) was made available in addition to the seasonal influenza vaccine.

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During the 2009–10 influenza season, nearly all influenza cases were due to the novel pH1N1 strain [12]. As many people received both the trivalent seasonal and the monovalent pH1N1 influenza vaccines, the prior receipt or coreceipt of the seasonal vaccine may have impacted the protectiveness of the pH1N1 vaccine by boosting or diminishing its efficacy. Several studies, including one study among US military personnel, showed that prior receipt of the seasonal vaccine offered some protection against the pH1N1 infection in 2009, especially against severe disease [13–17]. Other studies showed that prior or co-administration of the seasonal influenza vaccine did not provide any protection against the pH1N1 influenza [3, 18–21]. Some of these studies specified the formulation of the seasonal influenza vaccine. In contrast, some studies showed that prior or co-administration of the seasonal TIV influenza vaccine significantly reduced antibody response to the pH1N1 vaccine or increased the risk of pH1N1 requiring medical attention [22, 23]. In a Canadian study, there was a 1.4- to 2.5-fold increase in risk of laboratory-confirmed pH1N1 illnesses in 2009 among those who received the prior seasonal TIV in 2008–9 compared with controls [24].

In mice models, seasonal TIV prior to pH1N1 LAIV was comparable with receipt of one dose of pH1N1 LAIV alone, whereas seasonal LAIV followed by pH1N1 LAIV induced a robust response and complete protection from pH1N1 virus challenge in the upper respiratory tract [25]. This suggests a priming effect

by the LAIV formulation not seen with TIV. Subsequent studies evaluating the immunogenicity of pH1N1 included as a component of the seasonal influenza vaccine demonstrated adequate immunogenicity for all included strains [26].

Because of the potential impact on immunogenicity and effectiveness of the pH1N1 vaccine, and to provide critical information on the preferred vaccine formulation, understanding how influenza vaccine formulations potentially interact is of high clinical interest. Therefore, we performed a study comparing rates of influenza-like illness (ILI), influenza, and pneumonia in recipients of pH1N1 vaccine based on the seasonal vaccine status and type among US military members during the 2009–10 influenza season. Military members are a highly vaccinated population with universal healthcare coverage, which allow for this study. However, compared to the general adult population or a hospital-based sample, military members are younger, predominantly male, overall healthier, and potentially more geographically mobile.

METHODS

Study Population

This was an observational cohort study of all US military personnel aged 18–49 years, who were on active duty from 1 May 2009 to 30 May 2010 and stationed in the contiguous United States (Figure 1). Demographic and vaccination data were

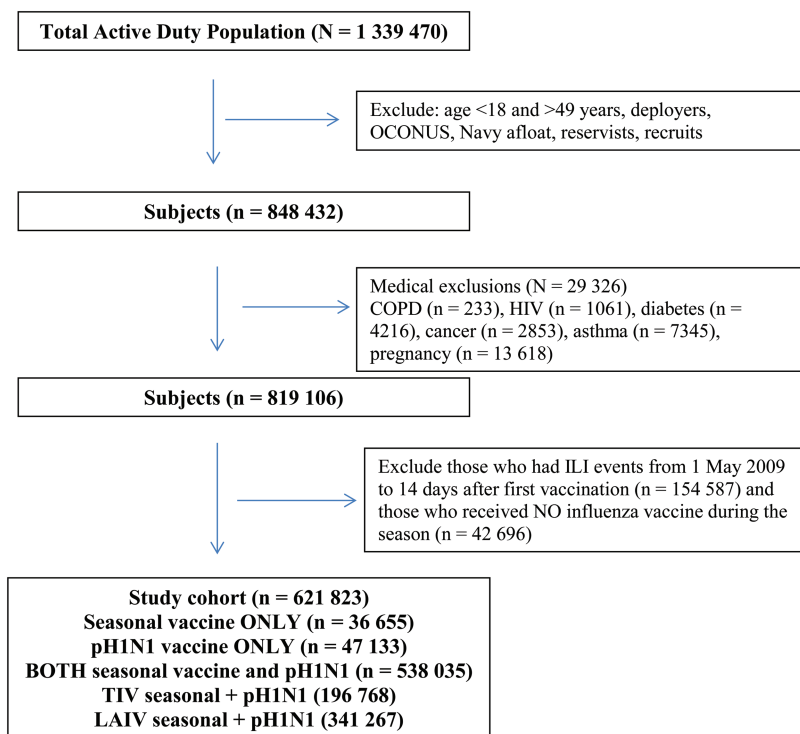


Figure 1. Inclusion and exclusion criteria during study period (1 May 2009 to 30 May 2010). Abbreviations: COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; ILI, influenza-like illness; LAIV, live, attenuated influenza vaccine; OCONUS, outside the continental United States; TIV, trivalent inactivated influenza vaccine.

obtained from the Defense Manpower Data Center, a collection of Department of Defense databases that contains longitudinal data including demographics, occupation classifications, and immunizations. Healthcare encounters, both outpatient and inpatient, and dispensed pharmaceuticals were obtained for this study cohort from the Military Health System Data Repository. Nonactive duty personnel, deployers, reservists, recruits, and members stationed on ships or overseas were excluded to ensure uniform influenza virus exposure risk and capture of health outcome data. Subjects were aged 18–49 years at time of vaccination, as LAIV is contraindicated in adults aged >49 years. In addition, those with contraindications for LAIV (pregnancy and significant comorbidities, such as human immunodeficiency virus, diabetes, asthma, chronic obstructive pulmonary disease, and cancer) were excluded, as this group may not mount an adequate response to the vaccination. Influenza vaccination is mandatory in the military, and waivers are rarely granted on stringent medical or religious grounds; thus, members who did not receive at least 1 influenza vaccine were also excluded. Lastly, as the pH1N1 pandemic started prior to vaccine availability and was the predominant circulating strain, subjects who were diagnosed with an ILI prior to 14 days after vaccination with any influenza vaccine were excluded because of the possibility they had already been infected with the pH1N1 virus and vaccine effects would not be demonstrated. Information on demographics, military characteristics, and comorbidities were included to identify potential risk factors for ILI. The study was approved by the Naval Health Research Center Institutional Review Board (NHRC.2014.0033).

Study Outcomes

Although laboratory-confirmed influenza is more specific, diagnostic testing was not frequently performed as recommended by the CDC during the pandemic; therefore, our primary outcome of interest was ILI events, which were defined according to a set of *International Classification of Disease, Ninth Edition, Clinical Modification* codes. These codes have been used in prior studies evaluating the correspondence of diagnostic codes to laboratory-diagnosed influenza (079.99, 382.9, 460, 461.9, 465.8, 465.9, 466, 486, 487, 487.1, 487.8, 490, 780.6, and 786.2) [27, 28]. The occurrence of any of these codes in the first 2 diagnostic fields were considered a single ILI event. If oseltamivir, zanamivir, amantadine, or rimantadine was dispensed, that was also considered an ILI event. As secondary outcomes, we studied diagnoses of influenza (487.0, 487.1, and 487.8) and pneumonia (486), which are included in the ILI diagnostic codes. If either influenza or pneumonia were used, additional relative risk analysis was performed.

Subjects were examined for outcomes over time, and results were stratified into several groups based on their first vaccination. Events from 1 May 2009 to <14 days after receipt of first influenza vaccine were excluded. Outcomes were captured

starting 14 days after receipt of their first influenza vaccination so the person would contribute to that group (eg, seasonal influenza vaccine). If a second vaccine was received at a later date, then 14 days after this second vaccination, the person would contribute to the group with that combination (eg, seasonal+pH1N1 vaccines). Only the first ILI event per person during the study period was used, and subjects were censored at that point for further events; however, they continued to be counted in the denominator for all members who served during the 12-month period.

Statistical Analysis

Descriptive statistics for all demographic variables and outcomes are presented as numbers (percentages) for categorical variables, with medians and means (standard deviations) for continuous variables. Univariable analyses, including χ^2 tests, were used to examine unadjusted associations of the study outcomes (ILI, influenza, and pneumonia cases) with vaccine combinations. Relative risk (RR) is presented for each main outcome by vaccine exposure. Confidence intervals and *P* values are not reported as this is a *population* analysis, that is, not a sample. All data analyses were completed using SAS software, version 9.3 (SAS Institute).

RESULTS

Study Population Characteristics

There were 1 339 470 members on active duty during the study period. The total cohort, after inclusion and exclusion criteria were applied, was 621 823 who received at least 1 influenza vaccine (either seasonal, pH1N1, or both) without preceding ILI (Figure 1). In this population, the average age was 28.5 years, 88.6% were male, 82.1% enlisted rank, and 74.3% had no more than a high school degree. The Army was the predominant service branch (43.3%), and most resided in the South (56.5%) (Table 1). A total of 36 655 (5.89%) service members received the seasonal vaccine only, 47 133 (7.58%) received the pH1N1 only, and the majority of this cohort—538 035 (86.53%)—received both the seasonal and pH1N1 vaccinations (Table 1).

Of the group receiving both the seasonal and pH1N1 vaccinations, there were 196 768 (36.57%) service members who received TIV+pH1N1, whereas 341 267 (63.43%) received LAIV+pH1N1 (Table 2). The median age was 27 years for both groups; however, the TIV+pH1N1 group included more subjects who were females; officers; serving in the Army, Coast Guard, or Marine Corps (compared with the Air Force); in a healthcare occupation; or residing in the South.

Outcomes

Influenza-like Illness, Influenza, and Pneumonia Events

Of all the subjects who received at least 1 influenza vaccine (621 823), 43 757 ILI events were diagnosed during the study period for an incidence rate of 7.04% (Table 1). Most subjects

Table 1. Study Population Characteristics and Outcome Data of Subjects, Aged 18–49 Years, Who Received at Least 1 Influenza Vaccine During the Pandemic H1N1 2009–2010

	Study Cohort		Seasonal Only		pH1N1 Only		Seasonal (Any) + pH1N1	
	n	(%)	n	(%)	n	(%)	n	(%)
Vaccination events	621 823	(100.0)	36 655	(5.89)	47 133	(7.58)	538 035	(86.53)
ILI event	43 757	(7.04)	4815	(13.14)	3043	(6.46)	35 899	(6.67)
Influenza	853	(0.14)	290	(0.79)	42	(0.09)	521	(0.10)
Pneumonia	1259	(0.20)	191	(0.52)	90	(0.19)	978	(0.18)
Demographics								
Age, mean (SD)	28.5	(73)	29.6	(78)	28.9	(76)	28.4	(73)
Median	27.0		28.0		27.0		27.0	
Age categories								
18–24	232 255	(37.4)	11 673	(31.8)	16 849	(35.8)	203 733	(37.9)
25–30	173 515	(27.9)	10 074	(27.5)	12 872	(27.3)	150 569	(28.0)
31–49	216 053	(34.7)	14 908	(40.7)	17 412	(36.9)	183 733	(34.2)
Sex								
Male	551 199	(88.6)	32 531	(88.7)	41 390	(87.8)	477 288	(88.7)
Female	70 624	(11.4)	4 134	(11.3)	5 743	(12.2)	60 747	(11.3)
Race								
Black	94 889	(15.3)	5568	(15.2)	6 776	(14.4)	82 545	(15.3)
White	411 589	(66.2)	23 863	(65.1)	30 798	(65.3)	356 928	(66.3)
Other	115 345	(18.5)	7 224	(19.7)	9 559	(20.3)	98 562	(18.3)
Service								
Army	263 181	(43.3)	9 734	(25.6)	15 541	(33.0)	237 906	(44.2)
Coast Guard	24 993	(4.0)	993	(2.7)	5 534	(11.7)	18 466	(3.4)
Air Force	159 391	(25.6)	5 997	(16.4)	6 272	(13.3)	147 122	(27.3)
Marine Corps	97 498	(15.7)	9 273	(25.3)	8 388	(17.8)	79 837	(14.8)
Navy	76 760	(12.3)	10 658	(29.1)	11 398	(24.2)	54 704	(10.2)
Rank								
Enlisted	510 678	(82.1)	28 221	(77.0)	37 485	(79.5)	444 972	(82.7)
Officer	111 145	(17.9)	8 434	(23.0)	9 648	(20.5)	93 063	(17.3)
Education								
≤High school	462 266	(74.3)	25 789	(70.4)	35 412	(75.1)	401 065	(74.5)
≥Some college	159 557	(25.7)	10 866	(29.6)	11 721	(24.9)	136 970	(25.5)
Occupation								
Infantry	143 106	(23.0)	8 487	(23.1)	10 395	(22.0)	124 244	(23.1)
Healthcare	52 248	(8.4)	1 789	(4.9)	5 280	(11.2)	45 179	(8.4)
Other	426 469	(68.6)	26 379	(72.0)	31 458	(66.7)	368 632	(68.5)
US geographical area								
Middle	78 683	(12.6)	4 185	(11.4)	3 227	(6.9)	71 271	(13.2)
Northeast	31 451	(5.1)	1 578	(4.3)	4 531	(9.6)	25 342	(4.7)
South	351 600	(56.5)	23 143	(63.1)	25 735	(54.6)	302 722	(56.3)
West	160 089	(25.8)	7 749	(21.1)	13 640	(28.9)	138 700	(25.8)

Abbreviations: ILI, influenza-like illness; SD, standard deviation.

received both the seasonal and pH1N1 vaccines (86.53%). The ILI rate for those who received only the seasonal vaccination was 13.14%, whereas those who received either the pH1N1 alone or in combination with the seasonal influenza vaccine had much lower rates (6.46% and 6.67%, respectively), resulting in a 49%–51% risk reduction (Table 3).

There were 853 cases of influenza and 1259 cases of pneumonia during the study period that included subjects who received at least 1 influenza vaccination (Table 1). In the group receiving the seasonal influenza vaccine only, there was an incidence rate of 0.79% for influenza and 0.52% for pneumonia, whereas the

group receiving pH1N1 alone had a rate of 0.09% and 0.19%, and the combination group had a rate of 0.10% and 0.18% (Table 1).

There were 521 cases of influenza and 978 cases of pneumonia in the group receiving both the seasonal and pH1N1 vaccines. The TIV+pH1N1 and LAIV+pH1N1 groups had similar rates of ILI (6.8% and 6.6%, respectively), influenza (0.10% and 0.09%, respectively), and pneumonia (0.20% and 0.17%, respectively) (Table 2). Compared with the seasonal influenza vaccine alone, pH1N1 reduced the risk for ILI (RR, 0.49), influenza (RR, 0.11), and pneumonia (RR, 0.37). The formulation of the seasonal influenza vaccine did not affect the efficacy of pH1N1 (Table 3).

Table 2. Study Population Characteristics and Outcome Data of Subjects Who Received Both Seasonal and Monovalent pH1N1 Influenza Vaccines

	Seasonal (Any) + pH1N1		Seasonal TIV + pH1N1		Seasonal LAIV + pH1N1	
	n	(%)	n	(%)	n	(%)
Vaccination events	538 035	(100.0)	196 768	(36.57)	341 267	(63.43)
ILI event	35 899	(6.67)	13 388	(6.80)	22 511	(6.60)
Influenza	521	(0.10)	197	(0.10)	324	(0.09)
Pneumonia	978	(0.18)	384	(0.20)	594	(0.17)
Demographics						
Age						
Mean (SD)	28.4	(7.3)	28.5	(7.3)	28.4	(7.3)
Median	27.0		27.0		27.0	
Age categories						
18–24	203 733	(37.9)	74 128	(37.7)	129 605	(38.0)
25–30	150 569	(28.0)	55 357	(28.1)	95 212	(27.9)
31–49	183 733	(34.2)	67 283	(34.2)	116 450	(34.1)
Gender						
Male	477 288	(88.7)	172 720	(87.8)	304 568	(89.2)
Female	60 747	(11.3)	24 048	(12.2)	36 699	(10.8)
Race						
Black	82 545	(15.3)	29 502	(15.0)	53 043	(15.5)
White	356 928	(66.3)	129 506	(65.8)	227 422	(66.6)
Other	98 562	(18.3)	37 760	(19.2)	60 802	(17.8)
Service						
Army	237 906	(44.2)	90 756	(46.1)	147 150	(43.1)
Coast Guard	18 466	(3.4)	10 315	(5.2)	8 151	(2.4)
Air Force	147 122	(27.3)	42 374	(21.5)	104 748	(30.7)
Marine Corps	79 837	(14.8)	33 618	(17.1)	46 219	(13.5)
Navy	54 704	(10.2)	19 705	(10.0)	34 999	(10.3)
Rank						
Enlisted	444 972	(82.7)	161 873	(82.3)	283 099	(83.0)
Officer	93 063	(17.3)	34 895	(17.7)	58 168	(17.0)
Education						
≤High school	401 065	(74.5)	148 433	(75.4)	252 632	(74.0)
≥Some college	136 970	(25.5)	48 335	(24.6)	88 635	(26.0)
Occupation						
Infantry	124 244	(23.1)	45 030	(22.9)	79 194	(23.2)
Healthcare	45 179	(8.4)	19 592	(10.0)	25 587	(7.5)
Other	368 632	(68.5)	132 146	(67.2)	236 486	(69.3)
US geographical area						
Middle	71 271	(13.2)	18 397	(9.3)	52 874	(15.5)
Northeast	25 342	(4.7)	8 293	(4.2)	17 049	(5.0)
South	302 722	(56.3)	116 244	(59.1)	186 478	(54.6)
West	138 700	(25.8)	53 834	(27.4)	84 866	(24.9)

Abbreviations: ILI, influenza-like illness; LAIV, live, attenuated influenza vaccine; TIV, trivalent inactivated influenza vaccine.

Table 3. Relative Risk (RR) of Influenza-like Illness (ILI), Influenza, and Pneumonia by Vaccine Type and Formulation

Outcomes	Seasonal Only (n = 36 655)			pH1N1 Only (n = 47 133)			Seasonal (Any) + pH1N1 (n = 538 035)			TIV + pH1N1 (n = 196 768)			LAIV + pH1N1 (n = 341 267)		
	n	(%)	RR ^a	n	(%)	RR ^a	n	(%)	RR ^a	n	(%)	RR ^a	n	(%)	RR ^a
ILI	4815	(13.14)	0.49	3043	(6.46)	0.51	35 899	(6.67)	0.52	13 388	(6.80)	0.13	22 511	(6.60)	0.50
Influenza	290	(0.79)	0.11	42	(0.09)	0.12	521	(0.10)	0.13	197	(0.10)	0.37	324	(0.09)	0.12
Pneumonia	191	(0.52)	0.37	90	(0.19)	0.35	978	(0.18)	0.37	384	(0.20)	0.37	594	(0.17)	0.33

Abbreviations: LAIV, live, attenuated influenza vaccine; TIV, trivalent inactivated influenza vaccine.

^aCompared with those receiving seasonal influenza vaccine only.

DISCUSSION

To our knowledge, this is one of the largest systematic analyses comparing the effect of formulation of the seasonal influenza vaccination on the clinical efficacy of the pH1N1 vaccination in a healthy adult population. In our highly vaccinated population with open access to medical care, there was no clinically significant difference in ILI, influenza, or pneumonia attack rates among those receiving the pH1N1 vaccine with or without receipt of the seasonal vaccine. Similarly, there was no clinically relevant difference in pH1N1 effectiveness between seasonal TIV and LAIV recipients. As with our other study, there were lower rates of ILI in Army and Marine Corps branches of service, infantry occupations, and officer rank, and higher ILI rates were observed in healthcare occupations and females [29]. Our study demonstrates that in healthy, young adults, regardless of seasonal vaccination status, immunization with the pH1N1 vaccination was effective in reducing the incidence of clinical encounters for ILI, influenza, and pneumonia compared with the seasonal vaccine alone.

As vaccination is the main preventive strategy for influenza, optimizing formulations and identifying factors that interfere with efficacy are vital. We recently showed that in a healthy, young adult population, there was no difference in rates of ILI, influenza, or pneumonia between the LAIV and TIV seasonal vaccine recipients over 3 consecutive influenza seasons. However, in another study, TIV was associated with fewer medical encounters when compared with LAIV [29–31].

Many studies have evaluated the impact of the prior season's influenza vaccine (2008–9), primarily TIV, on the pH1N1 vaccination or infection with conflicting results [13, 14, 16, 23, 24]. However, most of these studies focused on the first peak (April–July 2009) of the pandemic, whereas our study focused on the second peak (October 2009 onward) after the 2009–10 seasonal influenza vaccine and the pH1N1 monovalent vaccine.

There are multiple viral epitopes shared between the pandemic and seasonal H1N1 viruses, which may be involved in the priming effect, and thus, there is a plausible cross-reactive response [32, 33]. Compared with the swine flu in the 1970s where 2 doses of vaccine were needed to immunize a naive population, during the 2009 pandemic, 1 dose was sufficient in eliciting a protective response alluding to a prior vaccination or infection that primed them for adequate protection [34, 35]. When examining the epidemiology of the 2009 pandemic, it is clear that older populations were less affected due to prior exposure to antigenically related infection or vaccination. Therefore, identifying factors that produce a priming effect and enhance response is important in understanding how to improve efficacy of the influenza vaccine. When evaluating the possible impact of the seasonal vaccine formulation, there are very few studies that have examined this hypothesis. Animal studies by Chen et al are the only ones where there is a direct comparison of seasonal TIV and LAIV immunization prior to pH1N1 vaccination

[25]. In these elegantly designed studies, prior priming with either the seasonal LAIV or seasonal H1N1 infection, followed by a single-dose pH1N1 vaccine, produced robust serologic and cellular response to pH1N1 virus challenge, whereas seasonal TIV did not have this effect nor did a single dose of pH1N1 vaccination [25].

As demonstrated in other studies, infection with any strain of influenza produces a “short-lived strain-transcending immunity,” which is hypothesized to last between 3 and 6 months [36]. Therefore, those who were immunized during the 2008–9 season were less likely to get infected with the seasonal strain and subsequently had increased susceptibility to the pH1N1 infection by not having the temporary immunity from infection by the seasonal strain [36, 37]. In a study modeling this concept, Mercer et al supported this idea that risk was not from the vaccine itself, rather the prevention of infection that precluded the temporary immunity, although this was studied during the first wave of the pandemic [37].

There are potential reasons for variable immune responses to the different formulations. TIV production involves an inactivating step, which may destroy some of the antigenic epitopes, thus generating a more restricted immune response. This may potentially reduce common epitopes that could be important in the response to either the pH1N1 infection and/or vaccination. There are also different adjuvants used with TIV depending on the manufacture; in 1 animal study, the adjuvant in the seasonal influenza vaccine was associated with the priming effect [38]. Because LAIV is a live virus, which does not include an inactivating step, this allows for a wider range of immune response similar to that seen with natural infection. This may mechanistically provide a similar strain-transcending immunity compared with TIV, which provides more strain-specific immunity. There are experimental studies into pseudotyped influenza virus vaccines to induce immunity broadly among all strains with goals to create a universal flu vaccine [39, 40]. Laboratory measure of influenza vaccine response is typically limited to serology; however, other immune responses, such as other parts of adaptive immunity as well as innate immunity, are not currently examined in most vaccine studies. Furthermore, detected levels of antibody differ from neutralizing antibody responses, which may be associated with differing clinical outcomes. Short- and long-term immunity are mediated by differing mechanisms as well.

Potential limitations of our study included the impact of other variables on influenza rates over time beyond vaccinations (eg, public health responses and natural waning of infections over time); we anticipate these factors will be balanced between vaccine groups. Another potential limitation was that vaccination data were obtained from electronic records and subject to reporting errors and misclassification. However, we believe this was non-differential in nature. The reasons that some military members are vaccinated and the type of vaccine received may be subject to bias. On the other hand, because all military members have free

and open access to care and vaccine types are usually the result of availability issues, we anticipate these potential selection biases will be minimal. Our subjects received the 2 vaccines at variable times. Although most received the seasonal vaccination first, some received both at the same time; thus, duration of time between the 2 vaccines may affect potential interaction. As our study population was young, healthy, and highly vaccinated, there may have been less ILI, confirmed influenza, pneumonia diagnoses, and hospitalizations, which could have lessened our likelihood of capturing potential associations. Those with minor respiratory illness may not have sought medical attention, and subclinical infection would be missed in this analysis. In addition to being younger and generally healthy, military service members are a geographically diverse population and therefore may not reflect the general adult population or a hospital based sample, specific geographic regions, all demographics, or socioeconomic groups. We did not look for confounders and compare relative risk in our analysis. We did not study older adults (aged >49 years) or those with medical conditions that may affect their outcomes. Finally, our study was observational rather than a prospective, controlled trial. Thus, more research on the potential impact of formulation with laboratory-confirmed influenza, especially among healthcare workers, women, and more diverse populations, is warranted.

In conclusion, formulation of the seasonal influenza vaccination did not make a significant impact on diagnosis of ILI, influenza, or pneumonia. Our study clearly demonstrated that receiving the pH1N1 vaccine or vaccine combination containing the predominant circulating strain, pH1N1, was highly protective for preventing ILI, influenza, and pneumonia events in young, healthy adults. The potential impact of vaccine formulation and optimizing strategies must be considered in future planning and approaches to improve prevention.

Notes

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