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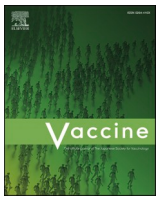

Predicting influenza vaccine-elicited antibody responses with practical point systems

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ABSTRACT

Introduction: Influenza vaccination plays a crucial role in reducing morbidity and mortality from influenza. However, its effectiveness varies due to multiple factors. Reliable point systems combining age, sex, BMI, vaccination history, and other baseline characteristics could aid in making evidence-based decisions regarding influenza vaccination.

Methods: Using human vaccination cohort data from the University of Georgia (UGA) over multiple influenza seasons, we developed two point systems: the Simple-Test score (STS) and the No-Test score (NTS). These scores predict vaccine-elicited antibody responses measured by hemagglutination inhibition (HAI) titers. Data from four influenza seasons (2016–2017 to 2019–2020) were used for model development and validation.

Results: The STS and NTS demonstrated good performance in discriminating between predicted lower-, moderate-, and higher-response groups. The AUC values for the STS were 0.943 for derivation and 0.841, 0.936, and 0.796 from the validation cohorts for 2016–2017, 2018–2019, and 2019–2020, respectively. Age, race, BMI, baseline HAI titers, and vaccination history significantly influenced the point system's performance. The point system showed robustness across age groups (teenagers, adults, and elderly). The AUC values for the NTS were 0.913 for derivation and 0.658 to 0.875 for validation datasets.

Conclusion: We successfully developed and validated two practical point systems to predict individual-level influenza vaccine-elicited antibody responses. These systems could facilitate personalized vaccination recommendations, policymaking, and resource allocation in influenza vaccination programs. The proposed point system is also a valuable tool for targeting populations that are likely to benefit most from influenza vaccination.

1. Introduction

Influenza vaccination contributes to mitigating morbidity and mortality due to influenza [1–4]. The Centers for Disease Control and Prevention (CDC) recommend routine annual influenza vaccination; however, its effectiveness is not consistently high, influenced by various factors. Some previous studies have raised questions about the benefits of yearly influenza vaccination [5–8]. The common and vital questions of 'Should I receive the flu shot this season?' and 'Should I recommend the influenza vaccine to Mr. Smith?' are queries faced by the general population and their primary physicians, respectively.

Antibody responses after vaccinations, albeit not perfect, are strongly correlated to protection against influenza, which may support evidence-based decisions to the aforementioned questions. The factors influencing the strength of vaccine-elicited antibody responses have been extensively studied. Aging stands out as a significant predictor, with the elderly exhibiting comparatively lower responses to influenza vaccines than their younger counterparts [9–11]. Gender differences also play a role, with females generally displaying higher antibody titers in response to vaccination than males [12–14]. Body Mass Index (BMI) is another crucial factor correlating with the induction of an immune response to influenza vaccines [15,16]. Additionally, an individual's

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vaccination history significantly impacts their antibody response [17–20]. Despite the importance of these factors, there has been limited discussion on creating a simple-to-use point system that consolidates these variables for the benefit of both the public and health professionals.

Clinical prediction rules (CPRs) have been instrumental in various fields, aiding in the prognosis of treatment effects and the subsequent severity of diseases [21–29]. Notably, there is a gap in the literature regarding the use of CPRs to predict vaccine-elicited antibody responses. In this study, we have developed a practical framework for predicting individual-level influenza vaccine-elicited antibody responses, offering a pathway for more personalized vaccination recommendations.

2. Methods

With human vaccination cohort studies from the University of Georgia, we developed and validated two sets of scores, the Simple-Test score (STS) and the No-Test score (NTS). Our primary outcome is the vaccine-elicited antibody responses. A hemagglutination inhibition (HAI) titers composite score was used as the dependent variable to generate our two sets of scores. We aimed to propose two sets of scores that can predict subjects' vaccine-elicited antibody responses measured by the HAI titers composite score.

2.1. The cohort studies

The human cohort vaccine study conducted in Athens, GA, USA, has been recruiting subjects annually since the 2016–2017 influenza season. Eligible subjects, including teenagers and adults who had not yet received the current seasonal influenza vaccine but may have a history of vaccination in previous seasons, were enrolled beginning in September of each year across four influenza seasons (2016–2017, 2017–2018, 2018–2019, 2019–2020). All participants volunteered for the study, with the lower age limit for the teenage group set at 11 or 12 years, depending on the cohort. The sera samples and host information were collected and investigated. Details have been published in a previous study [30].

The data covered four influenza seasons. In each season, standard-dose Fluzone quadrivalent influenza vaccines (QIV) were given to subjects. The influenza strains included in the vaccine formulation for the 2016–2017 season were A/ California/2009 (H1N1), A/Hong Kong/2014 (H3N2), B/Phuket/2013 (Yamagata-lineage), and B/Brisbane/2008 (Victoria-lineage). In the 2017–2018 season, the vaccine formulation had A/ Michigan/2015 (H1N1), A/Hong Kong/2014 (H3N2), B/Phuket/2013 (Yamagata-lineage), and B/Brisbane/2008 (Victoria-lineage). In the 2018–2019 season, the vaccine formulation included A/ Michigan/2015 (H1N1), A/ Singapore/2016 (H3N2), B/Phuket/2013 (Yamagata-lineage), and B/ Colorado/2017 (Victoria-lineage). In the 2019–2020 season, the included vaccine strains were A/ Brisbane/2018 (H1N1), A/ Kansas/2014 (H3N2), B/Phuket/2013 (Yamagata-lineage), and B/ Colorado/2017 (Victoria-lineage).

In total, 144, 255, 242, and 392 subjects were enrolled in the 2016–2017, 2017–2018, 2018–2019, and 2019–2020 influenza seasons, respectively. Serum samples at Day 0 prior to vaccination and at Day 21/28 post-vaccination were collected for assessing HAI activity. In addition, the study collected individual-level information, including age, sex, race, comorbidity, Body Mass Index (BMI), and prior vaccination history.

2.2. The HAI composite score

An HAI composite score was proposed to measure the overall homologous antibody responses across multiple strains elicited from a quadrivalent influenza vaccine (QIV) [30]. The score was created by summing the log2-scaled increasing folds of changes in HAI titers (pre-vaccination divided by post-vaccination) among the four influenza strains included in the vaccine formulation [30], following the formula below:

$$f(HAI) = \left(log_2\frac{HAI_{post}}{HAI_{pre}}\right)_{H1N1} + \left(log_2\frac{HAI_{post}}{HAI_{pre}}\right)_{H3N2} + \left(log_2\frac{HAI_{post}}{HAI_{pre}}\right)_{Bvic} + \left(log_2\frac{HAI_{post}}{HAI_{pre}}\right)_{Byam},$$

where $\boldsymbol{HAI_{pre}}$ and $\boldsymbol{HAI_{post}}$ are HAI titers measured pre- and post-vaccination. The HAI composite score can generate a binary outcome as vaccine elicited or vaccine non-elicited. Subjects whose HAI composite scores were greater or equal to 8 were classified as vaccine elicited, and those with an HAI composite below 8 were classified as vaccine non-elicited. The threshold of 8 corresponds to an average point of 2 in each strain, which is equivalent to a 4-fold change of HAI titers after vaccination, a widely adopted criterion for seroconversion in immunological studies of influenza. A recent study shows that each log2 unit increase in post-vaccination HAI against different influenza A vaccine strains provides a similar level of protection [31].

2.3. Two sets of scores

We built two sets of predictive point systems, namely the Simple-Test score (STS) and the No-Test score (NTS).

Independent variables used for constructing the STS include baseline HAI titers, subjects' age, race (White vs. non-White), comorbidity information (any comorbidity vs. none), BMI, and vaccination history in past seasons. The baseline HAI titer was the geometric mean of four vaccine strains' baseline HAI titers dichotomized by a threshold of 5.3, which is equivalent to log2 of a 1:40 HAI titer, a level considered to be associated with a 50 % reduction in risk against influenza infection [32]. The ages of subjects were measured in years and categorized into four groups ($<$18, 18–49, 50–64, and $\geq$65). The race variable was dichotomized into White vs. non-White. Comorbidity information was self-reported by the participants in each season at enrollment (including diabetes, asthma, hypertension, depression, anxiety, glaucoma, and other uncommon conditions). BMI was calculated by a person's weight in kilograms divided by the square of height in meters, and then categorized into three groups ($<$25, $\geq$25 and $<$30, and $\geq$30) [33]. Vaccination history was determined by whether an individual received a flu shot in the previous influenza season. For instance, in the 2016–2017 season, participants were asked if they received an influenza vaccination in the 2015–2016 season. A binary (vaccine non-elicited vs. vaccine non-elicited) logistic regression model was used to evaluate potential predictors in univariate analysis. Variable selections for predictors were processed with the stepwise method using likelihood-ratio test statistics with the threshold $p < 0.1$. The setting of threshold is to avoid the omission of important predictors due to statistical power. The standardized beta coefficients of the fitted multivariate model were used for generating scores. We first multiplied each beta (standardized) coefficient by 10 and then rounded the product to its nearest integer. The total point system score, hereby named the Simple-Test score (STS), is then calculated additively. The predicted lower-response, moderate-response, and higher-response groups were determined upon the score's distribution to create distinguishable groups potentially useful for clinical decision-making.

In addition, we applied the same methodology to explore a restrained point system without including lab measurement variables, specifically baseline HAI titers. We name it the No-Test score (NTS). NTS is considered more feasible in practical use.

2.4. Validation

Data collected in the 2017–2018 season were treated as our training dataset to generate scores. It was the first influenza season during which both teenagers and adult participants were enrolled. The scores'

performances were validated using datasets collected in the other three seasons (2016–2017, 2018–2019, and 2019–2020). We used the area under the receiving operating characteristic curve (AUC) to assess the derivation and validation datasets' overall discrimination/prediction.

There is no empty cell, blank, or any notation representing missingness in the data repository, and we did not find missing values using a data summary procedure "is.na()" in R software. All statistical analyses were conducted using R version 4.0.3 [34].

3. Results

3.1. Descriptive analysis

Descriptive statistics of all enrolled participants from 2016 to 2017 to 2019–2020 are presented in Table 1. Overall, White participants contributed over 80 % of the total sample size in most seasons. The percentage of teenagers in 2018–2019 (62.0 %) was much higher than those in the other three seasons. Consequently, the 2018–2019 influenza season had a relatively high proportion (64.0 %) of participants whose BMIs were below 25. In terms of HAI titers at baseline, participants in 2017–2018 were at higher levels (74.5 % of participants' baseline HAI titers were greater than or equaled to 5.3), and participants in 2019–2020 had much lower baseline HAI titers (71.9 % of participants' HAI baseline titers were lower than 5.3). Besides 2016–2017 when the cohort study started, more than 70 % of the enrolled subjects in each season were vaccinated in the previous influenza season. The exploratory analyses were presented in Fig. S1-S3.

Table 1
Descriptive statistics of subjects across seasons.

	2016–2017	2017–2018	2018–2019	2019–2020
Sample size	144	255	242	392
Age				
<18	0 (0 %)	72 (28.2 %)	150 (62.0 %)	99 (25.3 %)
≥18 and < 50	111 (77.1 %)	131 (51.4 %)	64 (26.4 %)	181 (46.2 %)
≥50 and < 65	21 (14.6 %)	30 (11.8 %)	17 (7.0 %)	91 (23.2 %)
≥65	12 (8.3 %)	22 (8.6 %)	11 (4.5 %)	21 (5.4 %)
Sex				
Male	56 (38.9 %)	113 (44.3 %)	105 (43.4 %)	160 (40.8 %)
Female	88 (61.1 %)	142 (55.7 %)	137 (56.6 %)	232 (59.2 %)
Race				
White	107 (74.3 %)	205 (80.4 %)	203 (83.9 %)	324 (82.7 %)
African American	14 (9.7 %)	19 (7.5 %)	11 (4.5 %)	33 (8.4 %)
Asian	8 (5.6 %)	6 (2.4 %)	6 (2.5 %)	7 (1.8 %)
Others	15 (10.4 %)	25 (9.8 %)	22 (9.1 %)	27 (6.9 %)
Comorbidity				
Yes	29 (20.1 %)	59 (23.1 %)	53 (21.9 %)	134 (34.2 %)
No	115 (79.9 %)	196 (76.9 %)	189 (78.1 %)	258 (65.8 %)
BMI				
<25	62 (43.1 %)	119 (46.7 %)	155 (64.0 %)	154 (39.3 %)
≥25 and < 30	52 (36.1 %)	75 (29.4 %)	50 (20.7 %)	127 (32.4 %)
≥30	30 (20.8 %)	61 (23.9 %)	37 (15.3 %)	111 (28.3 %)
Baseline HAI				
<5.3	84 (58.3 %)	65 (25.5 %)	106 (43.8 %)	282 (71.9 %)
≥5.3	60 (41.7 %)	190 (74.5 %)	136 (56.2 %)	110 (28.1 %)
Last season vaccination				
Yes	53 (36.8 %)	181 (71.0 %)	195 (80.6 %)	319 (81.4 %)
No	91 (63.2 %)	74 (29.0 %)	47 (19.4 %)	73 (18.6 %)
Composite score				
Median (IQR)	7 (3,13)	3 (1, 8)	3.5 (2, 6)	5 (2, 8)
<8	74 (51.4 %)	188 (73.7 %)	194 (80.2 %)	271 (69.1 %)
≥8	70 (48.6 %)	67 (26.3 %)	48 (19.8 %)	121 (30.9 %)

3.2. Development of the STS point system

In the univariable analysis (Table 2), we fitted logistic regressions to the 2017–2018 data. Younger age (<18) was an important predictor (OR, 7.08; 95 % CI, 2.18–32.03); Other variables showing additional predicting powers included the Non-White race (OR, 1.79; 95 % CI, 0.91–3.44), a BMI lower than 25 (OR, 2.56; 95 % CI, 1.27–5.48), not receiving an influenza vaccination in the previous influenza season (OR, 30.11; 95 % CI, 14.72–65.52), and a baseline geometric mean of HAI titers below 5.3 (OR, 10.78; 95 % CI, 5.69–21.03). We performed a multivariable logistic regression model using independent variables showing potential predicting powers in the previous step (age, race, BMI, baseline HAI, and prior vaccination history). The beta coefficients for each predictor are shown in Table 3. We then built a point system by assigning scores to each level of the predictors based on their corresponding beta coefficient. Each participant's total score was obtained by summing the individual score they had from each predictor, and cutoffs for three predicted response levels were determined. The final point system classified participants into predicted lower- (0–15 points), moderate- (16–27 points), and higher-response (28–44 points) groups (Table 4). Following the same scenario, we also generated a point system and corresponding classifications by linear regression model (Table S1 and S2).

3.3. Evaluation and validation of the STS point system

Table 4 and Fig. S4 show the performance of the point system in derivation and validation datasets. The value of AUC(s) was 0.943 from the derivation dataset and were 0.841, 0.936, and 0.796 from the validation cohorts from 2016 to 2017, 2018–2019, and 2019–2020, respectively. In the derivation cohort, the percentages of vaccine elicited were 3.8 %, 38.3 %, and 82.7 % in predicted lower-, moderate-, and higher-response groups, respectively. When the point system was

Table 2
Univariate analyses in the logistic regression model with 2017–2018 data.

Variables	Odds Ratio (95 % CI)	*P*-value
Age		
<18	7.08 (2.18, 32.03)	0.003
18–49	1.14 (0.35, 5.17)	0.843
50–64	1.58 (0.37, 8.28)	0.551
≥65 (ref)	1	
Sex		
Female (ref)	1	
Male	1.21 (0.69, 2.12)	0.509
Race		
White (ref)	1	
Non-White	1.79 (0.91, 3.44)	0.084
Comorbidity		
No (ref)	1	
Yes	0.84 (0.42, 1.62)	0.613
BMI		
≥25 and < 30 (ref)	1	
<25	2.56 (1.27, 5.48)	0.011
≥30	1.87 (0.81, 4.41)	0.146
Baseline HAI		
≥5.3 (ref)	1	
<5.3	10.78 (5.69, 21.03)	<0.001
Pre-vaccination		
Yes (ref)	1	
No	30.11 (14.72, 65.52)	<0.001

Table 3
Point system (STS) for the prediction of HAI composite scores derived from the 2017–2018 data using a multivariable logistic regression.

Predictor	Categories	Reference values (W_{ij})	β_i	Points
Age				
	<18	1	0.90	9
	18–49	2	0.22	2
	50–64	3	0.09	1
	≥ 65	0	0	0
Race				
	Non-White	1	0.28	3
	White	0	0	0
BMI				
	<25	1	0.36	4
	25–29	0	0	0
	≥30	2	0.36	4
Baseline of HAI				
	<5.3	1	1.19	12
	≥5.3	0	0	0
Pre-vaccination				
	No	1	1.55	16
	Yes	0	0	0

applied to the 2016–2017 validation dataset for the classification of predicted response groups, percentages of vaccine elicited were 8.1 %, 38.0 %, and 84.2 % in predicted lower-, moderate-, and higher-response groups, respectively. In the 2018–2019 cohort, the same validation procedure resulted in responding percentages of 1.5 %, 14.1 %, and 78.7 % in predicted lower-, moderate-, and higher-response groups. The corresponding percentages in the 2019–2020 validation dataset were 9.3 %, 31.2 %, and 77.9 %. Overall, separations were good in all four influenza seasons. In addition, the mean HAI composite score and its 95 % CI are presented in Table S3 for each influenza season. Generally, the mean HAI composite score was below 4 for the predicted lower-response group, between 4 and 10 for the predicted moderate-response group, and above 10 for the predicted higher-response group, further demonstrating good separations among the predicted response groups. Similar patterns can be observed in Table S4, where results were derived from another point system built by linear regression models following the same procedure.

Additionally, we tested if using multiple years as a derivation dataset in logistic regression would provide better results in classification and AUC. The points derived from a combined 3-year (2016–2017, 2017–2018, 2018–2019) dataset are presented in Table S5. Because the point of each host factor was similar to the results in Table 3, the classification followed the same thresholds (Table S6). The performance of the point system validated in 2019–2020 is shown in Tables S S6 and S7. The value of AUC was 0.788 from 2019 to 2020, which is close to the value for the same study year in Table 4. The mean of the HAI composite score and 95 % CI in Table S7 were also similar to the values in Table S3 corresponding to each predicted response level group.

3.4. Performance in age subgroups

We further tested the performance of the proposed point system in age subgroups. When using the teenage (12–18 years old), adult (≥18 & <65 years old), and elderly (≥65 years old) subgroups combining corresponding participants from all three validation cohorts (2016–2017, 2018–2019, 2019–2020), we obtained external validation AUCs at 0.822, 0.918, and 0.884 (Table S8). The mean HAI composite score and its 95 % CI presented in Table S9 also show good separations. The developed point system appears to be robust across age groups.

3.5. Prognosis value of baseline HAI and age

Among the predictors we identified, baseline HAI was the only predictor that requires lab tests. We assessed its predicting power as a sole biomarker. When building logistic regression models with only baseline HAI as the predictor, we obtained AUCs of 0.711, 0.742, 0.760, and 0.661 in 2016–2017, 2017–2018, 2018–2019, and 2019–2020 (Table S10). In addition, we assessed models using age as the only predictor and presented the AUCs in Table S10. The age-only models resulted in unsatisfactory AUCs of 0.556, 0.704, 0.693, 0.390 over the four influenza seasons.

3.6. A restrained NTS point system without lab measurement variables

Moreover, a restrained point system without laboratory testing variables was explored to facilitate general use in practice (Table S11). Based on previous variable selection results, age, race, BMI, and pre-vaccination records were kept when creating the new system. We followed the same procedure as previously described, and participants were categorized into predicted lower- (0–3 points), moderate-(4–19 points) and higher-response (≥20 points) groups (Table S12 and Fig. S5). The percentages of vaccine elicited were 6.4 % and 68.3 % in the predicted lower- and higher-response groups in 2017–2018. The classifications in the three validation datasets are included in Table S12.

Table 4
Response classifications across derivation and validation cohorts.

Predicted response level		2016–2017	*2017–2018	2018–2019	2019–2020
Lower	Vaccine elicited	3 (8.8 %)	6 (3.8 %)	2 (1.5 %)	14 (9.3 %)
	Vaccine non-elicited	34 (91.2 %)	150 (96.2 %)	129 (98.5 %)	137 (90.7 %)
Moderate	Vaccine elicited	19 (38.0 %)	18 (38.3 %)	9 (14.1 %)	54 (31.2 %)
	Vaccine non-elicited	31 (62.0 %)	29 (61.7 %)	55 (85.9 %)	119 (68.8 %)
Higher	Vaccine elicited	48 (84.2 %)	43 (82.7 %)	37 (78.7 %)	53 (77.9 %)
	Vaccine non-elicited	9 (15.8 %)	9 (17.3 %)	10 (21.3 %)	15 (22.1 %)
AUC		0.841	0.943	0.936	0.796

(Lower: <16; Moderate: 16–27; Higher: ≥28) (asterisk*: the derivation dataset; responding percentages in parentheses.)

The value of AUC(s) was 0.913 from the derivation dataset and were 0.728, 0.875, and 0.658 from the validation cohorts from 2016 to 2017, 2018–2019, and 2019–2020, relatively lower than those from the STS point system. The overall separations were also inferior to the results from the previous point system (Table S13). The restrained point system of multiple years derivation dataset is illustrated in Table S14. The performance validated in 2019–2020 of this restrained point system is presented in Table S6 and Table S7. The value of AUC was 0.672, which was slightly higher than the values corresponding to 2019–2020 in Table S12.

4. Discussions

We have successfully developed and validated point systems that can identify subjects with a low, moderate, or high probability of responding to the quadrivalent influenza vaccine. Derived from candidate variables in the UGA 2017–2018 cohort study, including age, race, BMI, HAI baseline titers, and vaccination histories, the point system yielded distinct proportions of vaccine elicited in each group: 3.8 % (predicted lower-response), 38.3 % (predicted moderate-response), and 82.7 % (predicted higher-response). Validation across different cohorts confirmed these distinct ratios. Additionally, our classification results, combining validation datasets across various age groups (teenagers, adults, and the elderly), demonstrated the robust performance of the proposed point system (all AUCs were greater than 0.8), indicating strong predictive accuracy regardless of age. Regarding the restrained point system without lab measurement variables, we had moderate performance in the validation datasets, particularly in the 2019–2020 influenza season.

The utility of clinical prediction rules in various medical domains has been well-established, aiding in medical diagnoses and informing health policymaking. Numerous studies have leveraged prediction rules to identify high-risk populations deserving prioritized treatment or medical care [25–27,35]. Notably, one study in particular utilized a clinical prediction rule to compare the benefits of different treatments for prognosis [24]. While our point systems do not predict the risk of infection or hospitalization, it could play an important role in targeting populations more likely to benefit from influenza vaccination. Our comprehensive point system demonstrates that nearly 80 % of participants classified in the predicted higher-response levels achieved a composite HAI score of 8 or higher across four influenza seasons. This feature provides physicians with valuable information for recommending flu shots to their patients. Beyond personalized vaccination schedules, targeting influenza vaccine beneficiaries has broader implications for policymakers, especially in resource-restrained countries or regions. Previous studies have indicated that a high dose of influenza vaccine is not only less costly but also more effective than a standard dose for the elderly [36,37]. By preparing the proper types of vaccines for specific populations, substantial cost savings and improvements in public health can be achieved. The point system presented in this study furnishes an efficient way to evaluate vaccine effectiveness across diverse demographic groups.

A previous study examined race-related disparities in antibody responses to influenza A virus among African Americans and White individuals aged 30 to 40 [38]. Intriguingly, African Americans exhibited higher immune responses compared to their White counterparts. The authors attributed this difference to imbalanced prior vaccination rates. Due to the lower number of young African Americans vaccinated prior to the study, their baseline neutralizing antibody titers were also lower than those of the White individuals. However, this distinction wasn't observed in participants aged 65 and older. Age is another recognized critical factor influencing human immunity, particularly in the context of antibody response to influenza vaccination [39–43]. Extensive prior research has consistently shown a diminished antibody response in older adults ($\geq$ 65 years of age). To assess age's impact within our point system, we conducted univariate analysis using age in the logistic regression model (Table S10). The AUC values from validation cohorts indicated poor discrimination in the univariate logistic regression, with the training dataset (2017–2018) yielding an AUC just above 0.7. Therefore, our simpler point system (NTS) still contains multiple factors rather than a single variable such as age. Moreover, the classification of elderly participants in each year is presented in Table S15. The results illustrate that the proposed point system can classify older adults into different response-level groups even when we pooled subjects of all age ranges together. Our findings highlight that individuals without prior vaccination are more likely to exhibit stronger HAI responses to the seasonal influenza vaccine. We believe this may open new avenues for exploring alternative vaccination strategies, such as biennial vaccination for certain groups. Also, this could be used to promote new influenza vaccine strategies in the group with poor vaccine elicitation – e.g., higher antigen dose, two influenza doses in the same season, and/or adjuvants. We view this study as an exploratory effort that aims to stimulate discussions on alternative vaccination strategies. Further research is warranted to evaluate the effectiveness of such strategies and their potential impact on clinical outcomes.

A pivotal strength of our study lies in the construction of the point system, utilizing an outcome variable that encompasses multiple influenza strains. This approach offers a comprehensive evaluation of influenza vaccine performance. Notably, our proposed point systems underwent external validations across multiple influenza seasons, demonstrating the robustness of our model in predicting the overall homologous HAI responses. This robustness is especially crucial given the variability in vaccine strains from year to year. Our developed point systems are also viable to apply to different age groups, and highly practical for implementation in outpatient or clinical settings. This adaptability enhances the applicability and utility of our model in diverse healthcare scenarios.

There are several limitations to this study. Firstly, the data we collected are from an observational study and had different participants and vaccines across years, which could introduce bias to the performance of our point system. With the White population comprising over 80 % in most seasonal cohorts (Table 1), the effectiveness of the point system for identifying more vulnerable racial groups is limited due to the scarcity of subjects from Non-White populations in our study. Moreover, the point system with better prediction performances still requires a lab test to get baseline HAI levels, and thus may not be practical for immediate use in the community. It is also crucial to note that our analyses did not account for the dose effect of the vaccine. While participants who received a standard-dose influenza vaccine were examined in this study, the performance of our point system for subjects receiving a trivalent high-dose influenza vaccine was not assessed due to limited sample size. Also, there was only a single type of influenza vaccine, and the outcome was limited to HAI responses in this study. Validating our point system with different types of vaccines and other immune biomarkers is important in the future. Type A and Type B influenza vaccine strains may not contribute equally to clinical protection [31,44]. While our model assumes equal weighting of each component, this assumption warrants further investigation. Connecting vaccine response to disease mitigation, especially for poor vaccine elicitation population, is important. Unfortunately, our dataset does not include information on infectious status or influenza-like illness (ILI), which limits our ability to explore the correlation between vaccine effectiveness and immune response directly. However, we acknowledge the importance of this connection, particularly in promoting new vaccination strategies such as higher antigen doses or adjuvants for populations that are less responsive to standard doses. Future research incorporating clinical outcomes related to ILI would be highly valuable in assessing the full potential of these alternative strategies.

5. Conclusion

We successfully developed and validated two practical point systems to predict individual-level influenza vaccine-elicited antibody responses. These systems could facilitate personalized vaccination recommendations, policymaking, and resource allocation in influenza vaccination programs. The proposed point system is also a valuable tool for targeting populations that are likely to benefit most from influenza vaccination.

CRediT authorship contribution statement

Ye Shen: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Meng-Hsuan Sung:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Yang Ge:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Yewen Chen:** Writing – review & editing, Writing – original draft, Investigation. **Michael A. Carlock:** Writing – review & editing, Writing – original draft. **Hannah B. Hanley:** Writing – review & editing, Writing – original draft. **Susan Jiang:** Writing – review & editing. **Andreas Handel:** Writing – review & editing. **Ted M. Ross:** Writing – review & editing.

Ethics statement

This study used secondary data and did not involve any personal information identifiable to individuals.

Code availability

The underlying code for this study is available in the supplementary materials.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2025.127737.

Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to the ongoing cohort study but are available from the corresponding author on reasonable request.

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