

### Abstract

**Background:** Risk factors for vaccine failure against medically-attended influenza are largely unknown. We examined these risk factors at BSWH for 3 seasons.

**Methods:** BSWH has been a CDC US Flu VE network site since 2011. We enrolled patients ages ≥6 months seeking outpatient care for acute respiratory illness (ARI) with cough; onset ≤7 days. Nasal-throat swabs were tested for influenza A&B by PCR. Subjects with vaccine failure and vaccinated controls were identified by influenza PCR results and EMR-verified vaccination ≥14 days prior to illness onset or first medically-attended ARI (MAARI). Subjects whose influenza status could not be ascertained were excluded. Multivariable logistic regression models were built using covariates with a p-value <0.2 in the univariate analysis. Odds ratios (OR) with 95% confidence intervals (CI) were computed.

**Results:** Out of 1445, 1035 and 1783 enrolled subjects during 2012-13, 2013-14 and 2014-15 seasons, we had 130, 53 and 153 PCR-confirmed vaccine failure cases, respectively. During 2012-13, age-group, health today, and inpatient stay during prior year were found to be significantly associated with vaccine failure. During 2013-14 and 2014-15, days from vaccination to illness onset, days from illness onset to enrollment, and prior season vaccination were significantly associated with vaccine failure.

**Conclusion:** The risk factors for vaccine failure against medically-attended influenza are age-group ≥65 years and prior season vaccination. Prior year inpatient stay, days from vaccination to illness onset and days from illness onset to enrollment had protective effects. Better and longer lasting vaccines are needed to prevent influenza.

### Background

- Annual influenza vaccination is recommended for persons ages ≥ 6 months in the US
- Seasonal vaccines are not always effective in preventing influenza
- Influenza vaccine failure may be associated with factors related to the virus such as antigenic drift and to the host such as immunosenescence associated with aging
- The CDC US Flu VE network is comprised of 5 sites in Michigan, Pennsylvania, Texas, Washington and Wisconsin

### Objective

- To investigate risk factors for vaccine failure by comparing vaccinated subjects with medically attended acute respiratory illness (MAARI) who test positive for influenza vs. those who test negative by PCR

### Methods

- **BSWH-Temple Population Research Area (TPRA): All residential zip codes in East Bell County, Central Texas**
- **Source population: Born before March 1 of each year, reside in BSWH-TPRA and have seen a primary care service provider for any reason in the past 3 years**
- **Prospective study of outpatients with acute respiratory illness of ≤ 7 days, with cough**
- **Tested combined nasal and throat swabs for influenza A&B by RT-PCR.**
- **Exclusion criteria: Received Oseltamivir (Tamiflu) or Zanamivir (Relenza) in the past 7 days**
- **Vaccination verified with electronic medical records**
- **To identify influenza vaccine failure cases and controls, we classified subjects who received routine medical care at our site with EMR-confirmed influenza vaccination based on influenza PCR results and MAARI visits (Figure 1)**
  - **Vaccine failure case definition:** Subjects with EMR-verified vaccination, influenza positive based on PCR result and vaccination 14 or more days prior to illness onset or first MAARI

#### Statistical Analysis:

- Descriptive statistics were compared between cases and controls with demographics, high risk medical conditions, vaccination status, type of vaccine administered, general health status, and the current health assessment using t-tests, Kruskal-Wallis tests, and chi square tests
- Univariate logistic regression models were used to assess the effects of covariates on the probability of vaccine failure
- Potential covariates included were age, gender, race or ethnicity, study site, smoking status, health status, health insurance, BMI, days from onset to enrollment, days from vaccination to onset, vaccine type, prior vaccination, and high risk medical conditions
- Each covariate was considered individually to assess its association with the likelihood of vaccine failure
  - If the p-value for a covariate was <0.2, it was considered for inclusion in the final model as it was marginally associated with the outcome
- A backwards selection procedure was used to build the final adjusted multivariable logistic regression model

### Results

Figure 1. Identification of Vaccine Failure cases and Controls for the 2012-13, 2013-14 and 2014-15 influenza seasons

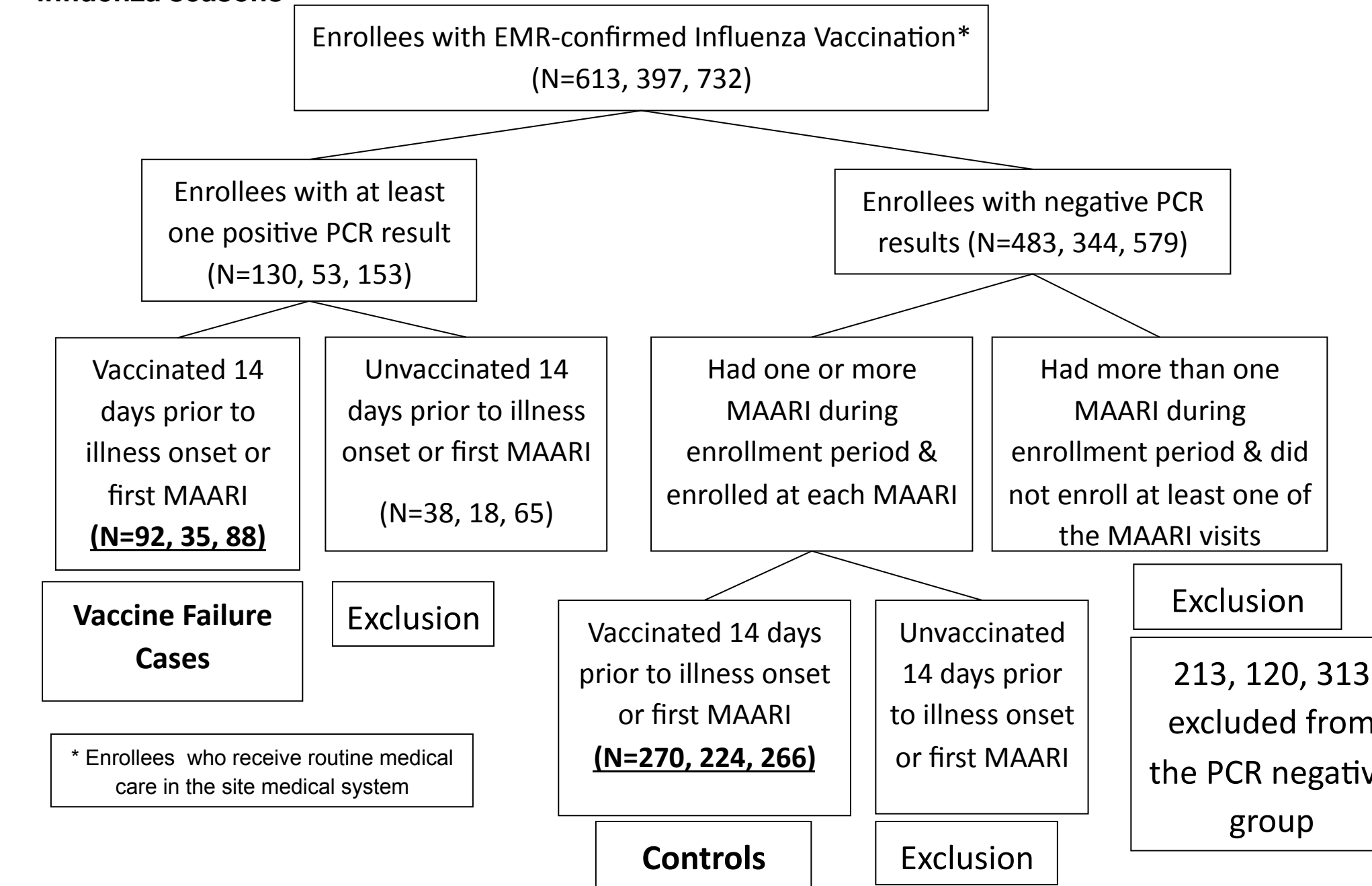


Table 1. Descriptive statistics of vaccine failure cases and controls

Year	Significant Patient Characteristics (p<0.05)	Cases N	Controls N	P-value		
2012-13	Age 65 years and older	21	22.8%	28	10.4%	0.003
	Five Age Groups*					0.032
	Health today (VAS** 0-100), Mean ± SD	45.7	22.9	54.0	21.8	0.002
	Chronic Liver Disease	4	4.4%	2	0.7%	0.039
	Malignancy	6	6.6%	3	1.1%	0.010
2013-14	Age at enrollment (in years), Mean ± SD	51.2	21.8	36.7	27.0	0.003
	Five Age Groups*					0.004
	Children 12 years old and younger	10	28.6%	111	49.6%	0.021
	Health Insurance					0.012
	Public	2	5.7%	64	28.6%	
	Private	27	77.1%	124	55.4%	
	Both	6	17.1%	35	15.6%	
Neither	0	0.0%	1	0.5%		
Days from vaccination to illness onset, Mean ± SD	95.1	27.8	111.2	39.0	0.004	
Days from illness onset to enrollment, Mean ± SD	2.5	1.5	3.1	1.9	0.043	
Prior Year Vaccination (born before 3/1/2012)	29	85.3%	137	64.3%	0.016	
2014-15	Age at enrollment (in years), Mean ± SD	51.2	21.8	36.7	27.1	0.003
	Health today, Mean ± SD	54	21.7%	60.7	22.4	0.015
	Days from vaccination to illness onset, Mean ± SD	82	35.9	107.1	44.9	0.000
	Days from illness onset to enrollment, Mean ± SD	2.5	1.4	3.6	1.8	0.000
	Prior season vaccination (born before 3/1/2013)	69	79.3%	160	64.3%	0.010

\* 6 months-8 years, 9-17 years, 18-49 years, 50-64 years and ≥ 65 years; \*\* Visual Analog Scale

Table 2. Summary of CDC-MMWR Influenza Season Activity Updates

Influenza Season (Severity)	Predominant A Subtype and B Lineage (%)
2012-13 (Moderately severe)	A(H3N2) (51%), B-Yamagata (36%), B-Victoria (10%)
2013-14 (Moderate)	pH1N1 (77%)
2014-15 (Moderately severe)	A(H3N2) (75%)

Table 3. Results of Adjusted Multivariable Logistic Regression Model

Year	Significant Variables (P-Value <0.05)	OR	95% CI	P-Value
2012-13	Age Group:			0.020
	6 months-8 years	1.21	(0.56, 2.56)	
	9-17 years	1.51	(0.68, 3.26)	
	18-49 years	Reference		
	50-64 years	1.12	(0.51, 2.47)	
≥ 65 years	3.91	(1.69, 9.06)		
Health Today		0.98	(0.97, 0.99)	0.002
Inpatient Stay*:	Yes	0.29	(0.09, 0.99)	0.048
	No	Reference		
2013-14	Significant Variables (P-Value <0.05)			
	Days from vaccination to illness onset	0.99	(0.98, 1.0)	0.012
	Days from illness onset to enrollment	0.76	(0.61, 0.96)	0.022
	Prior season vaccination:			0.049
	Yes	2.69	(1.01, 7.21)	
No	Reference			
2014-15	Significant Variables (P-Value <0.05)			
	Days from vaccination to illness onset	0.98	(0.98, 0.99)	0.000
	Days from illness onset to enrollment	0.67	(0.56, 0.79)	0.000
	Prior season vaccination:			0.013
	Yes	2.23	(1.19, 4.18)	
No	Reference			

\* Inpatient stay for a high risk condition in the year prior to enrollment

- Variables included but not significant
  - 2012-13: – Race and chronic lung disease
  - 2013-14: – Age group, white race and health today
  - 2014-15: – Household smoking and health today

### Conclusions

- Factors that increase the risk for influenza vaccine failure:
  - Age 65 years and older
  - Prior season vaccination
- Factors that decrease the risk for influenza vaccine failure:
  - Inpatient stay for a high risk condition in the year prior to enrollment
  - Days from vaccination to illness onset
  - Days from illness onset to enrollment
- More research is needed on effect of prior season vaccination on current season vaccine effectiveness

### Acknowledgement

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