Partial Protection of Influenza Vaccine in a Primary Care Population – Wisconsin: 2012-2015

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Background

Annual influenza vaccination is recommended routinely for all persons aged 6 months and older for the prevention of influenza.[1] Estimates of vaccine efficacy (VE) typically are calculated using a test-negative design: differential rates of laboratory-confirmed influenza illness among vaccinated and unvaccinated persons.[2] VE estimates for the last 10 seasons are summarized in the table, demonstrating a range from 10% to 60%.[3] The dichotomous outcome used in the test-negative design precludes an assessment of partial protection of influenza vaccination which could be characterized as milder clinical presentations in patients with laboratory-confirmed influenza.

We assessed clinical outcomes in primary care surveillance patients with laboratory confirmed influenza, based on vaccination status, to evaluate whether receipt of vaccine reduced the likelihood of having an influenza-like illness (ILI).

Influenza Season[1]	Reference	Study Site(s)	No. of Patients[2]	Adjusted Overall VE (%)	95% CI
2004-05	Belongia 2009	WI	762	10	-36, 40
2005-06	Belongia 2009	WI	346	21	-52, 59
2006-07	Belongia 2009	WI	871	52	22 ,70
2007-08	Belongia 2011	WI	1914	37	22, 49
2009-10	Griffin 2011	WI, MI, NY, TN	6757	56	23, 75
2010-11	Treanor 2011	WI, MI, NY, TN	4757	60	53, 66
2011-12	Ohmit 2014	WI, MI, PA, TX, WA	4771	47	36, 56
2012-13	McLean 2014	WI, MI, PA, TX, WA	6452	49	43, 55
2013-14	Unpublished	WI, MI, PA, TX, WA	5990	51	43, 58
2014-15	Flannery	WI, MI, PA, TX, WA	4913	19	7, 29

Methods

- The Wisconsin Influenza Incidence Surveillance Project (WIISP) conducted prospective surveillance in five primary care clinics (figure 1) of patients presenting with acute respiratory infections (ARI: >2 respiratory symptoms) from July 2012 through June 2015.
- A standard set of epidemiologic information and a nasopharyngeal swab were collected from each patient for influenza PCR.
- Receipt of influenza vaccine ≥14 days before the encounter was confirmed through patient chart audit with linkage to the Wisconsin Immunization Registry.
- Patients with PCR-confirmed influenza were categorized as meeting ILI criteria (fever with cough or sore throat) or having a non-ILI respiratory illness (figure 2).
- ILI has been shown in previous WIISP analyses to be associated with more severe clinical presentations (figure 3).
- We calculated the odds of ILI based on influenza vaccination status using binomial logistic regression, adjusting for age, time from illness onset, and sex. Analyses combined all seasons; individual season evaluation was limited by sample size.

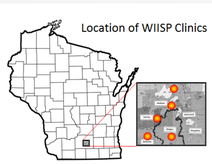

Figure 1.

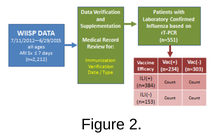

Figure 2.

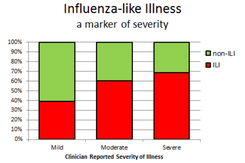

Figure 3.

Results

- Acute respiratory infection visits were recorded for 2,212 patients aged 18 days to 94.5 years (mean 34.8 years), of which 551 (24.9%) had laboratory-confirmed influenza. Among influenza-positive patients, 391 (71.0%) met the ILI case criteria.
- No significant differences were observed between influenza positive and negative patients in terms of age or sex. Influenza cases tended to present earlier after onset (p<0.001) than did influenza-negative cases; influenza cases were more severe (p=0.002) and were more likely to meet ILI case definition (p<0.001). Symptoms of influenza cases are displayed in figure 4.

Factor	Total (n=2,212)	Flu (-) (n=1,661)	Flu (+) (n=551)	Sign
Age (years)	34.8	34.5	36.2	NS
Sex (% female)	60.6	61.7	57.4	NS
Onset to visit (days)	3.8	4.0	3.5	p<0.001
Severity	1.74	1.72	1.80	p=0.002
ILI	53.8	48.2	71.0	p<0.001

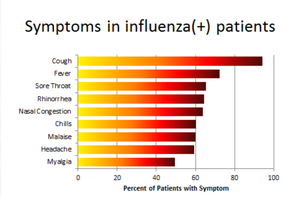

Figure 4.

	Influenza A (H1N1)	Influenza A (H3N2)	Influenza A unsubtypable	Influenza B
Number	112	286	5	146
Percent of Total	20.3	51.9	0.9	26.5

- The overall vaccination rate for WIISP surveillance patients was 48% (figure 5) which was higher than the general Wisconsin population (~35% for the same time period; figure 6). Similar age-specific patterns of vaccine receipt were noted between WIISP and the general Wisconsin population.

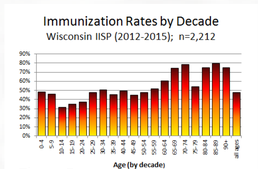

Figure 5.

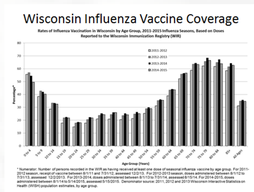

Figure 6.

Factor (ILI outcome)	OR	95% CI	Sign
Vaccine Receipt	**0.6388**	**0.4280 – 0.9534**	**p = 0.028**
Age (years)	0.9697	0.9597 – 0.9798	P < 0.001
Onset to visit (days)	0.9849	0.9369 –1.0353	NS
Sex (female)	0.9444	0.6316 – 1.4119	NS

- The odds of a vaccinated patient meeting ILI criteria as compared to unvaccinated was 0.639 (P=0.028; 95% CI: 0.428 – 0.9953), after adjusting for age, time from illness onset to clinic visit, and sex. Accordingly, there was a 36% reduction in ILI among vaccinees. No significant effects were seen for time from onset or sex; ILI significantly declined with advancing age.
- In post-hoc analyses, using specific symptoms as the outcome variable in binomial logistic regression, we found that previous receipt of vaccine in patients with confirmed influenza was associated with significant reductions in fever and chills, and significant increases in rhinorrhea. No vaccine effects were noted for cough, sore throat, malaise, myalgia, nasal congestion or headache.

Factor (fever outcome)	OR	95% CI	Sign
Vaccine Receipt	0.6147	0.4092 – 0.9234	p = 0.019

- We repeated the logistic regression analyses for each of three influenza seasons to assess for possible effects of specific strain / vaccine match effects. Of note was a 66% reduction in ILI for vaccinees with confirmed influenza in 2012/2013 during an influenza A(H3N2) outbreak, no effect in 2013/2014 with A(H1N1), and a non-significant 33% reduction during 2014/2015 – a season defined by influenza A(H3N2) with significant vaccine mismatch.

Season	Comment	OR	95% CI	Sign
2012/2013	Matched H3N2	0.34	0.16 – 0.72	P = 0.005
2013/2014	Matched H1N1	1.03	0.44 – 2.45	NS
2014/2015	Mismatched H3N2	0.67	0.37 – 1.22	NS

Discussion

- This study focused on individuals who had acute respiratory tract infections with laboratory-confirmed influenza and assessed clinical outcomes based on vaccine status.
- In the usual assessment of vaccine efficacy, these patients—had they received influenza vaccine–would reduce the estimated vaccine efficacy.
- We found that vaccinees—as compared to non-vaccinees—with laboratory-confirmed influenza manifest a significant 36% reduction in symptoms associated with Influenza-like illness. By extension, these cases appear to be less severe clinically.
- In post-hoc analyses, a reduction in fever appears to be the key symptom contributing to the reduced likelihood of ILI.
- The observed "partial protection" offered by influenza vaccines appears to vary by the dominant influenza strain and the level of vaccine match.
- This study is limited in that it is observational in nature, using a surveillance data set that was not created for the purpose of assessing vaccine efficacy.
- Nevertheless, the primary care population is representative of patients seeking medical attention for ARI and ILI. There was an extremely wide range in age across three influenza seasons and a variety of influenza strains.

Conclusions

- Influenza vaccines, when they fail to prevent influenza, likely contribute partial protection to vaccine recipients.
- This protection appears to result in less severe illness with less fever.
- New approaches to evaluating vaccine efficacy should be examined to provide a more robust assessment of the value of influenza vaccines in the general population.
- Such approaches could consider duration and intensity of symptoms.

References and Acknowledgements

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