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Major Article

Reasons for influenza vaccination underutilization: A case-control study

Scott S. Field MD [a,b,*]

[a] Pediatric Department, Huntsville Hospital, Huntsville, AL
[b] School of Medicine, University of Alabama, Birmingham, Huntsville, AL

Key Words:
Influenza
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Background: Influenza vaccines are underused.
Methods: Most (131/140) patients from a pediatric practice who were tested for influenza in the 2012-2013 season were enrolled. Medical records plus questionnaires determined vaccine and past disease histories and influenza vaccine attitudes. Influenza-negative tested cases (n = 65) and negative controls (n = 110) closely age-matched to 55 test-positive cases were compared with influenza-positive cases (n = 66) regarding prior influenza, vaccine efficacy, and limited vaccine season conflicting with birth dates and preventative visit timing to determine possible validity of reasons given for underutilization.
Results: The most common parental reason for not vaccinating was lack of perceived need. History of previous influenza was significantly ($P < .0001$) associated with disease. Live attenuated vaccine rates were greater in controls than in influenza patients for ages 2-18 years ($P < .005$) and for ages 6-18 years ($P < .0001$), whereas injectable vaccine rates were not ($P = .30$ and $P = .60$, respectively). Most positive cases (59%) and controls (89%) had no prior influenza.
Conclusions: Prior influenza disease may be a risk factor for infection that could influence vaccination benefit. Live attenuated influenza vaccine outperformed trivalent inactivated influenza vaccine. Limited disease experience in individuals with low influenza vaccination rates, along with vaccine efficacy limitations, lends validity to some underutilization.

Influenza is the most common potentially serious pediatric respiratory disease that might be prevented by immunization; however, the vaccines against it are frequently declined by parents. Surveyed pediatric (n = 105) and family care (n = 13) offices around the United States fully vaccinated 2%-53% of their children aged 6 months to 18 years for the 2010-2011 influenza season, with a median rate of 20%.[1] Reasons given by parents for not vaccinating children included low perceived risk of disease, limited vaccine effectiveness, and perceived vaccination side-effects, including the perception that the vaccine could cause influenza.[2] Effectiveness of available vaccines has indeed been limited[3]; however, head-to-head studies have found the nasally administered live attenuated influenza vaccine (LAIV) to be more efficacious than the injectable trivalent inactivated influenza vaccine (TIV) in children 6 months through 5 years of age.[4,5] Efficacy data for children 8-17 years of age are limited for both TIV and LAIV.[3]

Influenza morbidity is widely known, but there is limited information available about variability in susceptibility and age-related prevalence of disease in both vaccinated and unvaccinated populations. The primary objective is to shed light on why influenza vaccines are not more widely used. The secondary objective is to examine any validity to those reasons.

METHODS

Setting, participants, and design

A small suburban pediatric practice with approximately 1,600 active patients used rapid BinaxNOW Influenza A&B Card (Alere Scarborough, Inc., Scarborough, ME) test on nasopharyngeal swabs to diagnose patients suspected of having influenza. Testing was generally limited to patients with fever (>38°C), cough, or aching symptoms of <3 days duration during influenza season. All 140 patients tested between November 15, 2012, and March 31, 2013, were eligible to participate in the local institutional review committee–approved protocol using a written questionnaire asking about previous history of influenza, vaccination at other facilities (eg,

* Address correspondence to Scott S. Field, MD, 1106 Gleneagles Dr, Huntsville, AL 35801-6404.
E-mail address: scottfieldmd@gmail.com (S.S. Field).
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allergist, school, pharmacy), reasons for not vaccinating, and intention to vaccinate next year. Most (131/140) eligible patients participated. Medical records were reviewed to corroborate current and past influenza diagnoses and influenza vaccination history. Past laboratory logs were reviewed to corroborate test-positive disease history. Data were collected and analyzed by the author. The following factors facilitated determining issues of influenza susceptibility, prevalence, vaccine effectiveness, and vaccine acceptance: (1) a relatively stable population with known disease history, (2) detailed patient vaccination records, and (3) a season of high disease incidence in which surveillance isolates were well matched to vaccine strains.[6] Comparisons were made between influenza-positive patients and influenza-negative patients regarding reasons for not vaccinating, LAIV and TIV vaccine rates, and past vaccine and disease histories. Vaccines used for TIV were by Sanofi Pasteur (Kansas City, MO), and vaccines used for LAIV were by MedImmune (Frederick, MD).

Case enrollment and definition

Patients were enrolled by parental signed consent and questionnaire completion within 4 months of testing. Nine tested patients not enrolled were difficult to contact or did not complete consents or questionnaires within 4 months of testing. Five patients were tested twice in the season: 2 were negative both times, 2 were negative the first time and positive the second time, and 1 was positive the first time and negative the second time. Each twice-tested patient was only counted once, with positive testing counted preferentially. Nine patients had negative tests but had classical influenza symptoms and had close contact with family members who tested positive within 1 week of testing. They were considered false-negative cases. Two cases that tested negative developed a new illness about 2 weeks later and tested positive for influenza at different facilities; they also were counted as positive cases.

Nontested negative control selection

In addition to the 65 probable true test-negative controls, 2 age-matched (within 1 month) controls per test-positive patient were chosen (n = 110) for historical influenza and vaccination status comparison. The age-matched controls had no evidence of influenza this season and had detailed medical records for both clinical and vaccine histories.

Birth date analysis and comparative vaccination utilization

Vaccination rate comparisons were made between patients who were born inside versus outside of the preferred influenza vaccine season (August 1-December 15). Hepatitis (Hep) A vaccination status was also examined in tested patients and in age-matched controls for comparison of parent vaccination preferences regarding a relatively low-risk disease, Hep A, versus the much higher-risk disease, influenza.

Statistical analysis

Two-tailed Fisher exact testing was used for statistical comparisons. As an exploratory study, multivariate analyses were not done. $P < .05$ was considered significant.

RESULTS

Influenza types and season characteristics

Influenza A (n = 40) was the only type seen in December (starting December 3, 2012) and was not found after January 14, 2013. Positive tests for type B (n = 16) occurred from January 14, 2013-March 20, 2013.

Patient demographics

Tested ages ranged from 9 months to 18 years. Average age of all tested cases (8.72 years) was closer to that of age-matched controls (8.95) than their male to female ratios (1.05 vs 0.80) and their white to black ratios (12.2 vs 8.7). Average age in tested positive (9.0) versus tested negative (8.4) cases and male to female ratios (0.94 vs 1.17) was similar.

Questionnaire determined reasons for not vaccinating

Reasons for not vaccinating against influenza in a timely fashion are provided in Table 1. Responses were similar from parents of patients regardless of disease status. Other write-in reasons included "personal preference," "question effectiveness," "I get the flu when I get the shot," "has been sick," "prefer the immune system to develop naturally," "cost," "thought the early 2012 dose was still good," "no one in the family ever had flu without getting vaccinated," "did not want to introduce anything before traveling out of the country," and "like to get it more naturally." In response to the question regarding plans to get vaccinated next year, 46 of 66 (70%) positive cases responded yes, 12 (18%) responded no, and 8 (12%) responded maybe. Of the responses from the influenza-negative tested cases, 52 of 65 (80%) responded yes, 11 (17%) responded no, and 2 (3%) responded maybe. There were no significant differences in responses between influenza-positive and influenza-negative cases.

Past influenza history and vaccination status

Rates of those never vaccinated against influenza were comparable in the positive and negative cohorts (Table 2), but having been vaccinated before and missing vaccination this season were seen significantly ($P < .005$) more often in the positive than in each of the negative cohorts. Timely (at least 2 weeks before testing) LAIV administration occurred less often ($P < .005$) in the positive cohort, whereas timely TIV was found in comparable frequencies ($P = .30$) of the positive and negative cohorts. Excluding patients <6 years old, timely LAIV occurred in 4 of 49 (8%) positive cases compared with

Table 1
Reasons given for not vaccinating against influenza

Cohort	Test-positive (n = 57*)	Probable false-negative (n = 9)	Test-negative (n = 65)	All (N = 131)
Missed vaccine	42	7	30	79
Parent gave reason(s)	41	6	26	73
Did not think it was needed	21 (51)	1 (17)	9 (35)	31 (42)
Afraid of possible side-effects	15 (37)	2 (33)	10 (38)	27 (37)
Forgot or did not get around to it	17 (41)	2 (33)	10 (38)	29 (40)
Other	7 (17)	3 (50)	4 (15)	14 (19)

NOTE. Values are n (%) or n.
*Two cases tested negative but tested positive at another facility weeks later.

Table 2
Past and present influenza and vaccine status

Status	Positive patients* (N = 66)	Negative patients†		
		Tested (n = 65)	Nontested (n =110)	Total (N = 175)
Got LAIV ≥2 wk before test date	5(8)	18 (28)‡	43 (39%)§	61 (35)§
Got TIV ≥2 wk before test date	12 (18)	17 (26)	19 (17)	36 (21)
No vaccine ≥2 wk before test date	49 (74)	30 (46)‡	48 (44)§	78 (45)§
Never vaccinated against influenza	11 (17)	19 (29)	10 (9)	29 (17)
Vaccinated before, but not this year‖	37 (56)	19 (29)‡	28 (25)§	47 (27)§
Had influenza before this season	27 (41)	11 (17)‡	8 (7)§	19 (11)§
Had prior influenza, vaccinated this year	3/27 (11)	7/11 (64)‡	5/8 (63)‡	12/19 (63)‡
Had prior influenza, not vaccinated this year	24/27 (89)	4/11 (36)‡	3/8 (38)‡	7/19 (37)§
Had prior influenza, never vaccinated	4/27 (15)	0/11 (0)	2/8 (25)	2/19 (11)
No prior influenza	39 (59)	54 (83)‡	102 (93)§	156 (89)§
No prior influenza, vaccinated this year	14/39 (36)	28/54 (52)	45/102 (44)¶	85/156 (54)¶
No prior influenza, not vaccinated this year	25/39 (64)	26/54 (48)	45/102 (46)¶	71/156 (46)¶
No prior influenza, never vaccinated	7/39 (18)	9/54 (17%)	18/102 (18)	27/156 (17)

NOTE. Values are n/N (%) or n/n (%).
LAIV, live attenuated influenza vaccine; *TIV*, trivalent inactivated influenza vaccine.
*Includes enrolled test positive (n = 55), probable false negative (n = 9), and later test positive patients (n = 2).
†Includes enrolled influenza-negative patients (n = 65) and age-matched negative controls (n =110) of test positive patients. Test date for age-matched controls was the test date for their matching positives.
‡$P < .005$.
§$P < .0001$.
‖This year refers to those vaccinated between August 2012 and January 2013 at least 2 weeks before test dates.
¶$P < .05$.

Table 3
Influenza vaccination and disease associated with date of birth

Influenza status	Total	Favorable birth date* (n = 96)		Nonfavorable birth date† (n = 145)	
		Vaccinated‡	Not vaccinated§	Vaccinated	Not vaccinated
n (%)	241	52/96 (54)	44/96 (46)	62/145 (43)	83/145 (57)
Influenza positive	66	10/26 (38)	16/26 (62)	7/40 (17)	33/40 (83)‖
Influenza negative	175	42/70 (60)	28/70 (40)‖	55/105 (52)	50/105 (48)
Tested negative	65	13/23 (57)	10/23 (43)	22/42 (52)	20/42 (48)
Age-matched negative¶	110	29/47 (62)	18/47 (38)	33/63 (52)	30/63 (48)

NOTE. Values are n/n (%) or as otherwise indicated.
*Date of birth between August 1 and December 15, inclusive.
†Date of birth between December 16 and July 31, inclusive.
‡Received influenza vaccine at least 2 weeks prior to test date.
§Did not receive influenza vaccine at least 2 weeks prior to test date.
‖$P < .05$.
¶Negative controls age-matched to in-office test positives; vaccination timing based on test dates of matched test positives.

54 of 123 (43%) negative cases ($P < .0001$), whereas timely TIV occurred in 6 of 49 (12%) positive cases compared with 20 of 123 (16%) negative cases ($P = .64$).

Most enrolled patients (71%) had no previous history of influenza. Of 38 tested cases with previous influenza, 31 (82%) previous episodes were documented with positive rapid tests, and 7 were probable cases without laboratory confirmation. Lack of previous influenza in 54 of 65 (83%) negative tested cases and in 102 of 110 (93%) negative controls age-matched to the test-positive cases was significantly ($P < .005$) more common than in this season's positive cohort. In the age-matched cohort, 11 of 11 black patients and 88 of 96 (92%) white patients had never had influenza. In that cohort, 15% of white patients had never been vaccinated against influenza compared with 46% of black patients ($P = .02$).

Patients with no previous influenza disease or vaccination included 18 of 110 (16%) age-matched controls (13 patients >9 years of age) and 9 of 65 (14%) negative tested controls (5 patients >9 years of age) (Table 2). Of 11 positive patients who had never received an influenza vaccine, 7 (64%) got influenza for the first time, with ages ranging from 2-14 years old, with 4 patients <9 years old. Two patients <1.5 years old got influenza after appropriate vaccination (2 doses on time). There were no other positive cases after first-time vaccinations.

Comparative utilization of Hep A vaccine

Tested patients had received at least one dose of vaccine against Hep A (97/127; 76%) more often ($P = .02$) than having received an influenza vaccine in at least one of the past 3 seasons (82/131; 63%). Four of the tested patients were too young to receive Hep A vaccine.

Effect of birth dates on utilization

Patients who did not have influenza and had birth dates outside of the favorable (August 1-December 15) vaccination season were just as likely to be vaccinated as not (Table 3). Influenza-negative patients were more ($P < .05$) likely to be vaccinated if their date of birth was in that range. For influenza patients, nonfavorable birth dates were significantly ($P < .001$) associated with lack of vaccination, but that association was not significantly ($P = .08$) greater than that found with lack of vaccination in influenza patients with favorable birthdays.

DISCUSSION

Influenza is a potentially dangerous illness that has claimed the lives of at least 149 U.S. children in the 2012-2013 season alone[6];

however, the vaccines against it are poorly used.[7,8] In the patient population studied, influenza vaccines were used statistically less commonly than Hep A vaccine, even though the latter vaccine targets a relatively low-risk disease which gets much less attention than influenza. The 3 most common reasons by parents in this study for not immunizing children against influenza were (1) did not think it was needed, (2) afraid of possible side-effects, and (3) forgot or did not get around to it. The first and most common reason could encompass a belief that risk for contracting influenza is low in their family and that the vaccine offers little protection.

A reason rarely discussed in the medical literature why many parents do not think influenza vaccines are needed is the infrequency with which many individuals and families experience influenza first hand. In a 2010 Web-based influenza parental survey, 56% of parents said their child had never had it, whereas 13.5% of parents had never had it. Low perceived risk of influenza was listed as a reason by 46% for not wanting to vaccinate their children.[2] Most cases in the present study, whether positive or negative, had never experienced diagnosed (even unconfirmed suspected) influenza before, and approximately 18% of those had never been vaccinated against it. Most of the present study's influenza cases (39/66) experienced it for the first time, and 8 (21%) of those had never had an influenza vaccine. For such a common and contagious disease, it begs the question, why do not children experience influenza disease more commonly than they do? Having experienced influenza often convinces people to get vaccinated, but not always. The present survey found lower affirmative rates for plan to get vaccinated next year and more maybe responses from parents of positive cases than from those of negative cases. However, the results here indicate that having had influenza before may increase a child's risk significantly ($P < .0001$) for getting it again in the absence of vaccination. By contrast, patients not vaccinated who had no prior influenza history barely had significantly ($P = .048$) increased risk of getting infected.

Could some parents be right in saying that their child's risk of getting influenza without the vaccination is low? There is an established model of genetically determined innate resistance for gastrointestinal viruses, with a relatively common gene variant showing more protection than vaccine for rotavirus.[9] Natural or innate influenza resistance has biologic plausibility and could explain this study's finding of previous influenza as a potentially important modifier of vaccine efficacy and disease risk. Sialic acid–containing molecules in cell membranes lining the human respiratory tract act as receptors for the virus. Host cells with decreased sialic acid require high affinity hemagglutinin and decreased neuraminidase activity of the influenza virus for viral replication.[10]

The innate immune system also involves interferon, which can stimulate the expression of antiviral genes.[11] One such gene codes for interferon-inducible transmembrane (IFITM) protein, which interferes with viral entry.[12] Mice lacking IFITM3 get fulminant viral pneumonia from a normally low pathogenic influenza strain. A single nucleotide polymorphism (rs 12252) for IFITM3 with the CC variant, which lowers expression of IFITM3 protein, was overrepresented (5.7%) in hospitalized H1N1/09 influenza patients compared with that in a control population (0.3%).[13] The C allele is rare in Sub-Saharan African populations, which may relate to the lower vaccination rates among black patients because of their perceived and possibly true lower risks. This could partially explain the discrepancy in the literature and in this study between influenza vaccination rates in blacks versus whites. In an analysis of the Centers for Disease Control and Prevention's 2008 National Immunization Survey, black ethnicity was significantly associated with lower rates of influenza vaccination.[8] In the present study, never having been vaccinated against influenza was more common in black patients among age-matched negative controls, and all of them had never had influenza. Testing for rs 12252 composition in unvaccinated patients who do not get influenza versus patients who have had it more than once, and testing different ethnicity groups, may be helpful in determining a possible genetic basis of resistance.

Parents often question the effectiveness of influenza vaccines. Personal experience of ineffectiveness is supported in multiple TIV efficacy trials as reviewed in a 2012 meta-analysis.[3] LAIV was significantly more protective than TIV in the present study, which used a similar case-control design to a previous Centers for Disease Control and Prevention–collaborated influenza efficacy study.[14] That is consistent with prior studies for younger children,[3-5] but it also held true for 6-18 year olds in this study. More studies with larger numbers are needed to address that older age group. An alternative influenza shot using MF59 as an adjuvant is showing promise in providing better immunity (although more local side-effects) in 6- to 72-month olds, with 89% efficacy compared with 45% efficacy for the conventional TIV recipients.[15] The relative efficacy in 6- to 24-month olds favored the MF59 adjuvant by 75%. More research is needed to look at relative safety and efficacy of LAIV, MF59-enhanced injectables, and conventional split-virus injectables, especially in children <2 years of age.

Parental vaccine safety concerns often revolve around their personal influenza vaccine experience. Many studies have examined the adverse effects of influenza vaccines in children and have generally shown them to be safe with an adverse profile similar to placebo.[16,17] It is known that side-effects from both live and inactivated versions are greater with first doses, and whole-virus vaccines (only approved for adults) have more side-effects than split-virus versions.[17] It is possible that people who rarely if ever get vaccinated are more likely to have worse reactions when they agree to take the vaccine for the first time as adults. That may account for the frequently heard statement, "I never got flu except when I took the flu vaccine." What they perceived as flu was likely an adverse reaction rather than disease. Those reactions may be an important reason for influenza vaccine rejection and one that deserves further study. Adults who are rarely vaccinated against influenza may be best advised to get split-virus rather than whole-virus injectables. A previous parent survey found the perception that the vaccine could cause influenza (44%) and that the vaccine was not safe (24%) as reasons parents did not want to vaccinate.[2] Over a third of parents in the present study listed "afraid of possible side-effects" as a reason for not having vaccinated their child.

The influenza vaccine is the only immunization that is recommended yearly because of limited effective duration and changing viral strains. Influenza season generally lasts from December through March, which presents logistical problems for widespread utilization. The parents of patients who do not come for checkups yearly or whose birthdays come at other times of the year often forget or lack incentive to get their children immunized. More than half (56%) of the positive cases had been immunized in previous years but not before this influenza season. In the current study, patient birth date appeared to have some influence on vaccine utilization and, by extension, some protection from infection. Larger studies may find this to be of more significance.

Vaccines that have longer duration of action, such as the LAIV, may be useful in reducing the deleterious effect of missed vaccine years. One study showed some efficacy in the second season after 2 doses of LAIV were only given before the first season.[18] Waning immune response to influenza vaccines has limited data, but one study did indicate significantly less protection beyond 4 months of administration with TIV compared with LAIV.[19] Further studies are needed to provide policy guidance with regard to vaccinating with injectable influenza vaccine before October.

This study is limited by its retrospective design and small numbers. It is also unable to yield actual vaccine efficacies. It

involves only one influenza season and does not address possible changes with newer tetravalent vaccines. Parental recall concerning influenza history and symptom recall in tested patients was limited even though questionnaires were filled out within 4 months of the testing. Strengths include having complete clinical and vaccine records and being able to look at both disease histories and vaccination histories. To my knowledge, this is the first published study that looks at both of those factors, yielding highly significant new findings. This is also the first study, to my knowledge, that looks at the effect of birth date and limited vaccination season on vaccine utilization. Being an exploratory study with relatively small numbers, further validation by larger studies is indicated.

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