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RESEARCH ARTICLE

Annual Influenza Vaccination of Household Contacts of Immunocompromised Children with Kidney Disease

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Abstract

Background: Annual influenza vaccination (FV) is essential for household contacts (HC) of renal patients on immunosuppression (IS) to reduce secondary transmission. However, vaccination rates (VR) of HC are unknown. Our objective was to examine and optimize preventative strategies to improve them.

Methods: HC of pediatric renal transplant recipients (RT) and of those with nephrotic syndrome (NS), were surveyed on their (and their child's) vaccine status over 3 consecutive periods; A) 2014-2015 pre-educational intervention on FV importance, B) 2015-2016 post-educational intervention, and C) 2016-2017 without additional intervention.

Results: 15 RT ages 7-12 years old and 15 NS ages 4-19 years old were enrolled. 93% RT and 87% NS received FV in period A; 86% RT and 69% NS patients in period B; and 77% RT and 88% NS received FV in period C (accounting for lost follow ups). Household's fully vaccinated based on degree of patient IS: mild, moderate, severe were 36%, 20% and 45% respectively. Non- Hispanic households had higher VR compared to Hispanic households. In period C, 19% of caregivers were accepting FV who previously were not, however a total of 34% of caregivers did not receive FV despite prior education and reminders in the previous year.

Conclusions: Although children's vaccination rates were high, rates for household contacts were poor. More than 50% of caregivers reported reasons against FV; 1) confidence in their health, and 2) vaccines causing more harm than benefit. Post-educational intervention had minimal positive impact on FV rate. Families have FV misperceptions and underestimate the infectious risk they pose to their child.

Keywords: Influenza, Vaccine, Immunocompromised, Steroids, Nephrotic Syndrome

Abbreviations: IS: Immunosuppression; RT: Renal Transplant; FV: Annual Influenza Vaccination; HC: Household Contacts; NS: Nephrotic Syndrome; VR: Vaccination Rates

Introduction

Immunocompromised patients are more vulnerable to infection(s) compared to the general healthy population due to their underlying innate and/or adaptive or acquired immune deficit. In this group of patients, there is a strong emphasis towards preventative measures against various infections that can be taken whether it is via vaccination or chemoprophylaxis [1]. Influenza is an important cause of morbidity following organ transplantation [2]. Close contacts and family members should be immunized fully, and, in particular, should receive influenza vaccine yearly [3]. However, it is unclear how does guidance are implemented in practice.

In this report we addressed Influenza vaccination in household contacts of immunocompromised children with kidney disease in single suburban medical center. The target group included children with nephrotic syndrome or renal transplant recipients. Both conditions lead to an acquired immunodeficiency, secondary to use of immunosuppressants post-transplant or, due to the underlying disease process (i.e. for those with nephrotic flares exposed to steroids, while experiencing physiologic intermittent excretion of protective serum immunoglobulins).

Influenza virus was chosen as the focus for prevention against infection due to its common and predicted circulation on seasonal basis. Since influenza is a major cause of death for vaccine preventable diseases, with an unpredictable peak time, vaccination should be pursued on annual bases as it serves as a simple form of protection from this virus. Antigenic drift and shifts is a viral defense mechanism unique to influenza, disguising itself to host immune system despite being exposed in past and thus, makes it vital for annual vaccination to increase the best chance of matching the virus circulating for

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the current season. Considering a good match between the circulating strain and vaccine strain, the risk for flu-related illness is decreased by 40-60% among the general population who is vaccinated [4].

The highest rate of infection has been seen on the extreme ends of age, this being young children and the elderly. The risk for flu related complications, including viral or bacterial pneumonia, hospitalization and death [1] and for renal transplant patient, acute allograft rejection [5]. The consequences increases with younger age and/or high risk medical conditions such as asthma, cardiovascular, renal, metabolic, endocrine diseases, long term aspirin use and the immunocompromised [6] (Table 1).

CDC/ACIP and IDSA recommends all transplant and immunocompromised patients to receive the inactivated flu vaccine yearly, including household members and health care workers close in contact which these individuals [7, 8].

Given a less robust immune system function in the immunocompromised host, the humoral immune response to any vaccine is likewise compromised. In one study, the rate of sero-conversion to protective antibody responses was decreased in renal transplant patients for which booster vaccines were required, though cell mediated immunity was found to be comparable to healthy controls [9]. Viral clearance is controlled mainly by CD8 cells, which are able to identify hemagglutinin epitopes of the virus along with other internal proteins [10]. Unlike obtaining vaccine protective serum titers, routine screening of viral specific cell mediated protective immunity is limited as it is not readily performed in commercial labs. Nonetheless, vaccine immune responses of immunocompromised patients are unclear, and may be suboptimal. Thus, it is essential for close contacts to protect themselves from this virus, also referred to as the 'cocooning effect' [11].

Our hypothesis is influenza vaccination rates (VR) of HC in children are unknown, and our objective was to examine and optimize preventative strategies to improve them, honing in on the vulnerable immunocompromised renal pediatric population.

Methods

We used Quality Improvement design, survey study. Households of RT and NS patients were surveyed via phone calls to determine vaccine status of household members, including the patient. Patient demographics, immunosuppressive therapy and influenza illness history, if any, was obtained via chart reviews. Vaccine status and reasons for or against receiving flu vaccine was determined for seasons: A) 2014-2015 (pre education), B) 2015-2016 (post education) and C) 2016-2017 (no intervention). (See Appendix: Study Questionnaire). Education was provided on importance of flu vaccination via phone discussion, mailed flyers and phone call reminders with the next approaching influenza season. The primary outcome was to determine VR of our patients' close contacts based on ethnicity, patient classified degree of IS (defined as mild if exposed to 2 or less IS, no rejection/ relapse within 1 year of study start or in remission; moderate if exposed to 3 or more IS drugs, rejection or relapse > 6 months from study start; severe if rejection or relapse < 6 months from study start, or within first year post transplant, or recent NS diagnosis) and to understand the influence of education on vaccine compliance. The secondary outcome was to identify the factors which influence caregivers to receive or refuse vaccinations for themselves or their child.

Results

Fifteen RT patients aged 7-12 years old and 15 NS patients aged 4-19 years old were followed. (See Appendix: Table 2 Demographics) One RT and 2 NS patients were lost to follow-up. For season 2014-2015, 93% RT and 87% NS received FV; in season 2015-2016, 86% RT and 69% NS patients received FV (Figure 1). Overall, VR in HC based on degree of patient IS were 36%, 20% and 45% for mild, moderate, and severe IS, respectively (Figure 2). Non-Hispanic households had higher VRs compared to Hispanic households (Figure 3). During season 2015-2016, 62% of those with cold-like symptoms had

Age, Years	Hospitalization Rate Per 100,000 Persons	
	With High-Risk Medical Conditions	Without High-Risk Medical Conditions
≤4	3562	509
5-14	274	39
15-64	873	125
65-74	4235	605
≥75	8797	1257

NOTE: Data are from the Centers for Disease Control and Prevention. High-risk medical conditions are as defined by the Advisory Committee on Immunization Practices [2]- that is, chronic disorders of the pulmonary or cardiovascular systems, including asthma; immunosuppression; metabolic or endocrine disorder; long-term aspirin therapy; renal disease; pregnancy; and hernoglobinopathy.

Table 1: Hospitalization rates for patients, by age and risk group (interpandemic years) [6].

DEMOGRAPHICS	Renal Transplant Recipients (n=15)	Nephrotic Syndrome (n=15)
Age in years		
<5	0 (0%)	2 (13%)
6-15	6 (40%	9 (60%)
16-20	8 (53%)	4 (27%)
>21	1 (7%)	0 (0%)
Gender (M:F)	1.5 : 1	2:01
Ethnicity		
Hispanic (n=13/30)	9 (60%)	4 (27%)
Non-Hispanic (n=15/30)	6 (40%)	9 (60%)
History of Influenza-confirmed events	4 (27%) 1 subject requiring ICU stay	3 (20%) 1 subject with annual flu

Table 2: Demographics.

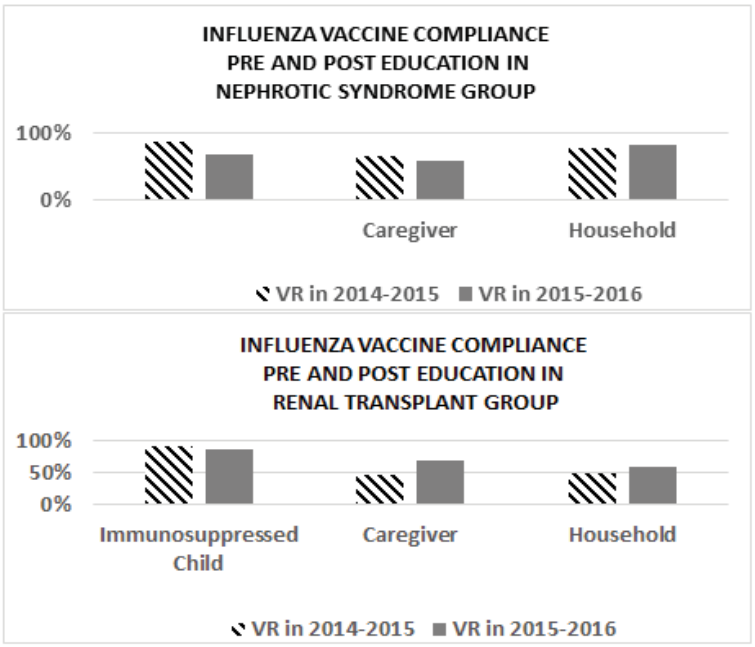

Figure 1: Comparing VR pre and post education for RT and NS patients.

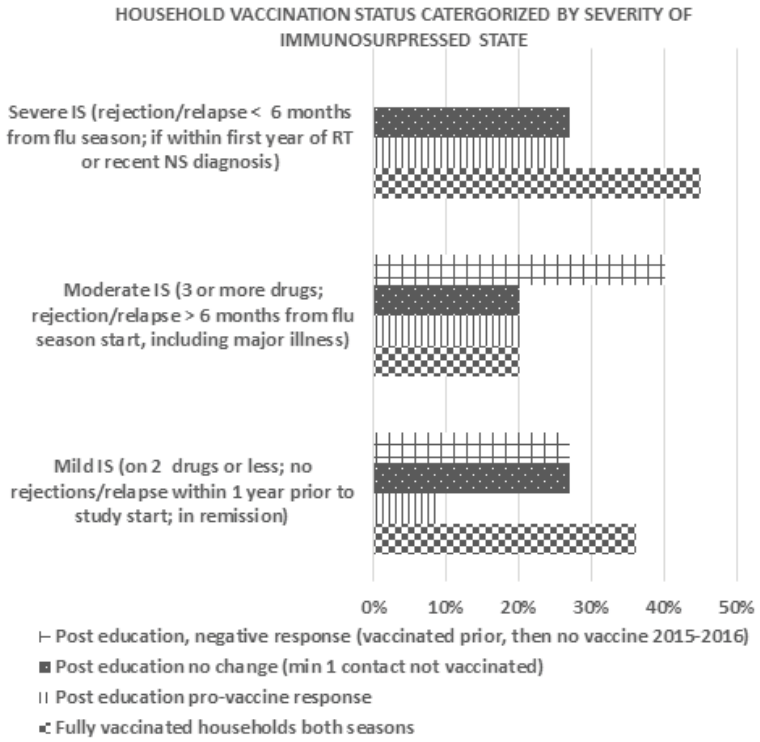

Figure 2: Comparing VR by degree of IS.

at least 1 household contact that did not receive FV.

In the third consecutive season 2016-2017, this time without any preceding re-education or reminders to families, there were 9/30 families lost to follow up. Of the 21 households left to interview, 10/21 (47%) received the vaccine as typically does to help avoid sickness or from PMD recommendation; 4/21 (19%) improved their vaccine acceptance status response due to better vaccine availability at clinics or jobs, insurance coverage or time convenience; 2/21 (10%) did not receive the vaccine due to complaints of being too busy or being ill. 5/21 (24%) continued to not pursue the vaccine due to lack of trust in vaccine, no personal concerns he/she will be affected by the flu given no prior flu illness, too busy or simply did not wish to without any explanation provided.

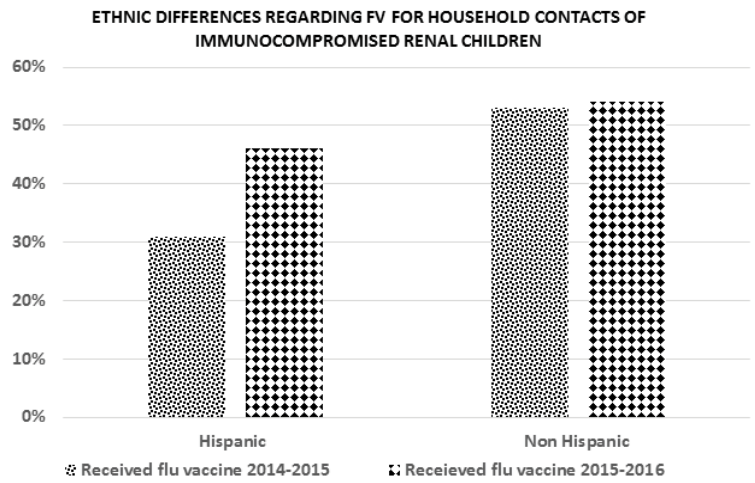

Figure 3: Comparing VR by ethnicities.

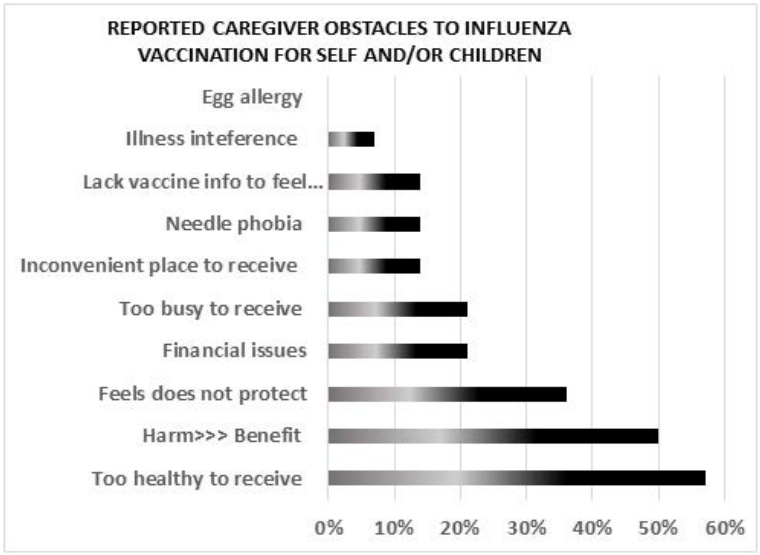

Figure 4: Caregiver obstacles to FV for self and/or child (Supplemental).

More than 50% of caregivers reported that their reasoning against receiving FV was confidence in their own good health and additionally, that vaccines cause more harm than benefit (Figure 4). Ninety-two percent reported physician advice to be the most influential factor regarding pro-vaccination. Face-to-face and phone calls were preferred by these caregivers to discuss this important topic.

Discussion

Our VR of HC was consistently lower than VR of children with nephrotic syndrome or renal transplant. Among family members of children with mild, moderate or severe IS, those who were classified with severe IS were more likely to be compliant with vaccination, while vaccine education did not positively influence the households of children with only mild or moderate IS. A subconscious awareness of one's child being 'sick' or more 'medically fragile', may explain a more of a prompt attitude towards vaccination this particular subgroup of families.

Hispanics demonstrated a prominent change in VR (16 % increase vs 1 % in non-Hispanic households) post education, which may suggest when time is carefully allotted to education and ensuring verbal understanding of what is being said to non- English speaking families (using a language interpreter), this proves to be accommodating. Only a small percentage of caregivers believe the importance for self-vaccination to protect their children. At the same time, the chief reason for caregivers to vaccinate was due to physician advice, thus physicians can play a major role in educating and changing the perspective of their patient's families. There were no confirmed Influenza cases diagnosed during this 3 year study period in those with symptomatic flu like symptoms who sought medical attention.

In immunocompromised children, the humoral immune response post vaccination (of any vaccine) is likely to be variable on individual bases since degree of immunosuppression is also variable, depending on

severity of underlying condition and the type and quantity of exposure to IS regimen/medication. Study analyses found, for example, transplant recipients on MMF to have significantly lower sero-conversion compared to other IS agents [5, 12]. Consequently, it cannot be assumed protective immunity is established in such high risk individuals based on the receipt of vaccination alone. As a future next step, to confirm protective immunity, a pilot study to obtain influenza hemagglutinin titers 4 weeks post vaccination in our patients, would be a simple method to determine who may still require a booster vaccine for optimal protection for the duration of the season. Furthermore, a randomize multi-center study could be carried out to recruit immunocompromised individuals to receive either the routine vaccine dose or a higher vaccine dose, such has been done in a phase III trial using *Fluzone* in solid organ transplant patients [11], followed by titers obtained 4 weeks later to compare immunogenicity responses.

Limitations

Due to the small sample size of this study with some subjects also lost to follow up, the significance of results could not be analyzed.

Conclusion

VR of HC was poor. More than 50% of caregivers reported not feeling the need to receive the FV because they were generally healthy individuals, in addition to concerns for the vaccine causing more harm than benefit. 92% reported physician advice most influential factor regarding pro-vaccination. Face-to-face discussions and phone discussions are preferred.

Post educational intervention had only a minimal positive influence in encouraging caregivers to receive the FV. We surmise this may have been due to vaccine mismatch from the season prior, decreasing the confidence in the vaccine to protect against the flu. Regardless, families have FV misperceptions and underestimate the infectious risk they pose to their child, and thus would require ongoing education for benefits of the FV.

Conflict of interests

The authors of this manuscript have nothing to disclose.

Acknowledgements

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Appendix

Study Questionnaire

Questionnaire for Household Contacts of Immunocompromised Renal Patients

Patient age: _____

Patient gender: _____

1. **What medical diagnosis does your child have?**

a) If transplant patient, was donor living or deceased? Living / Deceased

b) If living donor, is this donor a household contact? Y / N

2. **What medication(s) is your child taking, if any?**
3. **Has your child ever been diagnosed with the Influenza A or B viral illness (confirmed)?** Y / N

If yes, when: _____

4. **Has your child received flu vaccine this past season?** Y / N

If yes, when: _____

If no, what is the reason: _____

5. **Have you as the caregiver received flu vaccine this past season?** Y / N

If yes, when:_____

If no, what is the reason: _____

6. **Has other household contacts > 6 m/o old received flu vaccine this past season?** Y / N

If yes, when: _____

If no, what is the reason: _____