Olfactory disorders are highly prevalent in the general population, affecting 2 to 5 million adults in the United States, and may arise from hundreds of different etiologies. The most common associated conditions include inflammatory or infectious sinonasal disease, head trauma, toxin exposure, endocrine or metabolic derangements, neurodegenerative conditions, and upper respiratory tract infections (URIs). The frequency of olfactory dysfunction following URI varies from 18% to 42%. Olfactory loss after viral infection is often temporary but may be permanent. The ability to smell, and therefore taste, has an impact on multiple activities of daily life. Olfaction greatly influences the desire for food as well as satiation after eating, serves as a warning signal against noxious chemicals and spoiled food, and contributes to environmental awareness and appreciation. Loss of smell has been shown to have a negative impact on mood, social interactions, and overall quality of life (QOL).

Olfactory loss may be caused by various respiratory viruses, including the influenza virus. Because of the highly contagious nature of seasonal influenza and its associated morbidity and mortality, seasonal vaccination programs have been instituted in this country and around the world. Although there are more than 200 subtypes of viruses associated with the common cold, and not all have been studied in relation to olfactory loss, there is evidence showing that the influenza virus does cause direct damage to the olfactory epithelium. Although the exact mechanism of olfactory loss following influenza infection is not completely understood, direct damage by the virus and indirect damage caused by the ensuing inflammatory response to olfactory neurons and supporting cells are likely mechanisms. Because viral infections are a primary cause of olfactory dysfunction, the objective of this study was to investigate whether patients who received the influenza vaccine within a set time period were less vulnerable to developing permanent olfactory dysfunction.
Patients have either post-URI or idiopathic etiology for olfactory loss, stable or worsening for at least 3 mo

Patients with obstructive, inflammatory, neoplastic, traumatic, neurodegenerative, metabolic, endocrinologic, or medication or toxin exposure etiology for olfactory dysfunction, and those with symptoms < 3 mo (documented via endoscopy, imaging, and medical record review)

Patients form control group from age-, sex-, and race-matched rhinology patients also seen from March 2013 to March 2014

This flowchart demonstrates the number of patients first selected out by inclusion criteria and then exclusion criteria, as well as the formation of our control group and the further weaving of participants based on access to all pertinent data points. ICD-9 indicates International Classification of Disease, Ninth Revision; SNOT-22, 22-item Sinonasal Outcomes Testing questionnaire; URI, upper respiratory tract infection.

Methods

We performed a retrospective medical record review and telephone survey using a matched case–control design to assess the relationship between smell dysfunction and influenza immunization status. Institutional review board approval was obtained from Emory University. Any patient who presented to our tertiary rhinology practice within 1 year, from March 1, 2013, to March 1, 2014, with a primary complaint of smell dysfunction was initially included in this study. We found these patients using International Classification of Disease, Ninth Revision (ICD-9) diagnosis code 781.1, and then reviewed the responses from the 22-item Sinonasal Outcomes Testing (SNOT-22) QOL questionnaire. Patients had to identify item 21 (“sense of taste/smell”) on the SNOT-22 QOL scale as the primary and most important complaint (ie, a level 5, with no other questions receiving higher response than a 2) in order to be included in the study. This means that any patient who presented with symptoms consistent with major or minor criteria for chronic rhinosinusitis or symptoms of allergic rhinitis were automatically excluded. Using sinonasal endoscopy and imaging results found in the medical record (because all patients presenting with smell dysfunction underwent both endoscopy and magnetic resonance imaging), patients with either obstructive or neoplastic etiologies for their smell disturbance were further excluded from this study, as were patients who had not experienced stable or worsening olfactory dysfunc-

Results

Using ICD-9 diagnosis codes, SNOT-22 results, and medical record review for a patient population seen from March 2013 to March 2014, we identified a group of 42 patients with subjective olfactory dysfunction occurring after URI or from idiopathic cause using the criteria described herein. Six patients in the olfactory dysfunction group had incomplete medical records or were not able to be contacted via telephone; therefore, a total of 36 of the 42 patients in the olfactory dysfunction group were included in the study. Their ages ranged from 34 years to 84 years (mean, 57 years). Race/ethnicity breakdown consisted of 1 Asian, 15 black, 1 Hispanic, and 19 white patients. There were 23 female and 13 male patients (Table 1). The etiology of olfactory dysfunction was found to be post-URI in 12 (33%) and idiopathic in 24 (67%). Duration of olfactory loss ranged from 3 to 48 months (mean, 19 months).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
</tr>
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<tbody>
<tr>
<td>Age, mean (range), y</td>
<td>57 (34-84)</td>
</tr>
<tr>
<td>Male</td>
<td>13 (33)</td>
</tr>
<tr>
<td>Female</td>
<td>23 (67)</td>
</tr>
<tr>
<td>Race/ethnicity*</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Black</td>
<td>15 (42)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>White</td>
<td>19 (53)</td>
</tr>
</tbody>
</table>

* Percentages do not total 100% because of rounding.
A careful selection of a control cohort gave us 42 age-, sex-, and race-matched patients who had also been seen in the rhinology division over the same time period but who did not experience olfactory concerns. Four patients in the control group of 42 also either had incomplete medical records or could not be contacted via telephone, leaving 38 patients to include in the study. After exclusion of patients with incomplete medical records and those unable to be reached by phone, differences in demographics with a difference of n = 2 between groups were nominal, adding 1 black and 1 white patient to the control group, and 1 more each of female and male sex. Age range and mean remained consistent between the 2 groups.

No patients in the study received an intranasal vaccination; thus, we were unable to perform any analysis regarding method of vaccination. Seven of 36 (19%) in the olfactory dysfunction group received the vaccine in the year prior to presentation, compared with 16 of 38 (42%) in the control group. χ² Testing showed a statistically significant difference (P = .04) (Table 2). Cramer’s ϕ was then used to show effect size, which demonstrates what practical significance our statistically significant data have. Our ϕ value was 0.25, which shows a small to moderate effect size.

### Discussion

Olfactory disorders are common and are likely underdiagnosed. As outlined herein, smell dysfunction affects almost all aspects of daily life. Those with smell disorders have reported feeling vulnerable to potential safety hazards, such as smoke and carbon monoxide.1,2,9 Others have reported worries of poor personal hygiene.6 Even the simple act of eating and drinking with friends and family becomes a forced activity instead of bringing enjoyment to the patient, resulting in poor QOL, mood changes, and depression, which have been frequently demonstrated in this patient population.8,10

One of the most common causes of permanent olfactory dysfunction in adulthood is URI, making up 18% to 42% of the clinical population.2-4 Post-URI olfactory loss more commonly affects women than men and those 40 to 65 years old.9,11 Unlike other etiologies of olfactory disorders, most patients with post-URI loss experience sudden olfactory loss.6 URIs are also one of the most common causes of dysosmia, or the distortion of smell.1,6 Unfortunately, the natural progression of this disorder shows only approximately one-third of patients showing improvement in olfactory function after 1 year.9

The exact viral agents responsible for smell loss have not been elucidated. The seasonality of post-URI olfactory dysfunction suggests that influenza or parainfluenza viruses may be causative agents. Other viral candidates include rhinovirus, picornavirus, human coronavirus, and Epstein-Barr virus.2,11,12 Seasonal influenza affects 5% to 15% of the population in the northern hemisphere.13 Influenza viruses are highly contagious respiratory viruses that are transmitted directly by exposure to large, virus-containing respiratory droplets (ie, generated by a cough or sneeze) or indirectly by contact with contaminated surfaces followed by self-inoculation of ocular, nasal, or oral mucosa.14

<table>
<thead>
<tr>
<th>Subjective OD</th>
<th>Vaccinated</th>
<th>Not Vaccinated</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>With</td>
<td>7 (19%)</td>
<td>29 (81%)</td>
<td>.04</td>
</tr>
<tr>
<td>Without</td>
<td>16 (42%)</td>
<td>22 (58%)</td>
<td></td>
</tr>
</tbody>
</table>

The mechanism of olfactory loss is incompletely understood, although we do know that intranasal inoculation results in virus localization to the olfactory bulb.7 The influenza virus can cause cell death by direct infection with cell lysis and the release of new virions, or it can induce apoptosis.5 In addition, virus-infected cells secrete a multitude of proinflammatory cytokines and chemokines, resulting in an influx of inflammatory cells, such as dendritic cells, neutrophils, and macrophages, that are activated to kill the virus and remove infected host cells by phagocytosis. Damage to bystander cells is thought to occur commonly, and more virulent viral strains induce a greater proinflammatory cascade. Extensive airway epithelial cell destruction is a frequent outcome of influenza virus infection.7,13 In keeping with its exposed location, olfactory epithelium would certainly be in the path of this cell destruction.

Owing to the burden of disease and associated morbidity and mortality associated with influenza infection, vaccination is considered the primary strategy for prevention and control of influenza.45 Annual influenza vaccination is recommended in the United States for all health care workers, all children older than 6 months, all adults 50 years or older, all people with chronic medical conditions, pregnant women, and contacts of these people.16 There are 2 types of vaccines available in the United States. Inactivated influenza vaccines have been available since the 1940s, and are administered via intramuscular injection to anyone older than 6 months.15,16 A live attenuated, cold-adapted influenza vaccine was developed in the 1960s and has been available in the United States since 2003. This vaccine is administered via intranasal spray and is appropriate for a selected population.16 Live attenuated vaccines have been shown to be more effective than inactivated vaccines in their ability to induce local mucosal immune responses in addition to systemic responses.57,58 The effectiveness in preventing laboratory-confirmed influenza with either mode of vaccination when the vaccine strains are well matched to the circulating strains is 70% to 90% among children and young healthy adults.16,19

Intranasal immunization has been shown to attenuate viral localization and inflammatory mediator upregulation in the olfactory bulb at least 24 hours after infection in a murine model.8 Unfortunately, none of the study patients had received the influenza vaccine via intranasal administration. Thus, we are unable to comment on whether the method of administration has any bearing on subjective olfactory function in humans, but this is certainly an interesting area ripe for future investigation.

Limitations of this study include its retrospective nature and the need to rely on patient recall for some cases. There are biases inherent in any retrospective review, and we acknowledge these as a limitation of this type of study. Although there are objective smell tests available to document the level of olfactory dysfunction a patient may have, there is no upfront...
screening questionnaire that is validated for this use. Therefore, although the SNOT-22 questionnaire was not designed as an olfactory screening tool and has only 1 of 22 questions related to smell, we used this along with the ICD-9 code as preliminary steps before embarking on full medical record review. We also acknowledge that the major limitation of this study is that identification of the olfactory dysfunction patient group was based on subjective findings, and no smell test was performed to verify hyposmia and/or anosmia. In our practice up to this point, we have usually reserved objective smell testing for patients with Workers’ Compensation issues or patients suspected of malingering because there has been no well-established intervention we can offer these patients. However, as new possible treatment options, such as olfactory training, emerge for treatment of olfactory dysfunction it will certainly become more useful to apply these validated objective tests for use in pretreatment and posttreatment scenarios. Because of these limitations, we can only view these subjective findings as preliminary data, and future studies using a larger patient population and monitoring for olfactory dysfunction prospectively after the administration of influenza vaccine would be beneficial to elucidate if there is a real relationship to be studied there.

Conclusions

There is currently no well-established, effective treatment for post-URI olfactory dysfunction. With more than 200 subtypes of viruses associated with the common cold, more than 200 causes of olfactory loss, and in the setting of a retrospective study, there is no way to know for sure if the patients in our study experienced olfactory loss due to influenza virus, some other virus, or from some other etiology completely. We only wish to show this association as a jumping-off point for further investigation, and by no means are we attempting to indicate causation. We do not know the number of individuals who experience olfactory loss directly from influenza virus, and it may only be a small percentage of patients presenting with anosmia or hyposmia that these data can be applied to. The results of this study show that influenza vaccination is associated with a significantly reduced rate of subjective olfactory dysfunction, but we do not have objective or prospective data at this time to demonstrate causation. This is simply a preliminary finding that we hope to use as a starting point for future research to examine the role of influenza and influenza vaccination in patients with olfactory loss.

REFERENCES