## High Intensive Care Unit Admission Rate for 2013–2014 Influenza Is Associated with a Low Rate of Vaccination

*To the Editor*:

Influenza causes significant morbidity and mortality (1–3). Effectiveness of the vaccine and severity of the clinical manifestations of infection are highly variable each year. The rate of influenza vaccination in the United States has increased in recent years but remains poor (4, 5). We have previously reported our experience in the intensive care unit (ICU) with influenza A, H1N1 pandemic 2009 virus (pH1N1) (6, 7). We now report our initial observations for the 2013–2014 influenza season. We observe a very high number of otherwise healthy individuals with critical illness requiring care in the ICU. Most patients who required ICU level care were not previously vaccinated.

To determine whether patients requiring ICU care have a lower rate of vaccination prior to hospitalization, we reviewed the records of all hospitalized patients who tested positive for the influenza virus by polymerase chain reaction assay at our institution between November 1, 2013, and January 8, 2014. Basic patient demographics and underlying risk factors for severe influenza are provided (Table 1). The median age in our cohort was 28.5 years (range: 2 mo to 101 yr), similar to the age distribution observed during the 2009–2010 influenza season (8).

We have observed a dramatic increase in the number of hospitalizations and ICU admissions in recent weeks (Figure 1A). The majority of patients (48/55; 87.3%) were infected with pH1N1, consistent with recent Centers of Disease Control and Prevention (CDC) reporting (9). Only one case of influenza H3 and one case of influenza B were observed.

Thirteen of 55 (23.6%) patients were vaccinated against influenza at least 2 weeks prior to the onset of their acute illness. The vaccination rate in hospitalized patients appears lower than the CDC-reported early-season vaccination rate of 36.5% for the 2012–2013 and 39.5% for the 2013–2014 periods (5). Furthermore, the rate of influenza vaccination in patients requiring ICU care was lower than in patients admitted to general wards: 9.1% (2/22) of patients requiring ICU admission were vaccinated, compared with 33.3% (11/33) of patients treated in non-ICU settings ($P = 0.053$; odds ratio = 5.0 [95% confidence interval (CI), 0.98–25.4]) (Figure 1B). Similarly, 8.7% (2/23) of patients who required either mechanical ventilation or bilevel positive airway pressure were vaccinated, compared with 34.4% (11/32) of patients who did not require positive pressure ventilation ($P = 0.051$; odds ratio = 5.5 [95% CI, 1.084–27.90]) (Figure 1C). Of the two patients admitted to the ICU who did receive influenza vaccination, one had chronic lymphocytic leukemia and was receiving rituximab, likely impeding an adequate immune response to vaccination; the second patient had hepatitis C and ethanol abuse and was admitted to the ICU overnight for alcohol withdrawal. Of the 11 patients who were treated in the non-ICU setting and received influenza vaccinations, 9 could be considered immunocompromised due to a variety of conditions, including hematologic malignancy, solid organ transplant, liver cirrhosis, renal failure, and use of medications known to suppress the immune system. Together, these observations support that vaccination may provide protection from severe illness requiring hospitalization and is in agreement with previous reports (10, 11).

**Table 1:** Patient Demographics

| Patient Characteristics | Number (Percentage) |
|---|---|
| Age, median (range) | 28.5 (2 mo to 101 yr) |
| <18 yr old | 4 (7.3) |
| 18–49 yr old | 27 (49.1) |
| 50–64 yr old | 18 (32.7) |
| ⩾65 yr old | 6 (10.9) |
| Sex | |
| Male | 33 (60.0) |
| Female | 22 (40.0) |
| Race/ethnicity | |
| White | 26 (47.3) |
| African American | 23 (41.8) |
| Hispanic | 3 (5.5) |
| Other | 2 (3.6) |
| Native American | 1 (1.8) |
| Body mass index ⩾ 30 | 22 (40.0) |
| Current tobacco use | 19 (34.5) |
| Comorbidities* | |
| Pulmonary disease | 23 (41.8) |
| Diabetes mellitus | 12 (21.8) |
| Cardiovascular disease | 10 (18.2) |
| Renal disease | 8 (14.5) |
| Other immunosuppression† | 6 (10.9) |
| Neuromuscular disorder | 3 (5.5) |
| Solid organ transplant | 3 (5.5) |
| Hematologic malignancy | 3 (5.5) |
| Pregnancy | 2 (3.6) |

*Subjects may have more than one underlying condition.
†Immunosuppressive condition other than solid organ transplant and hematologic malignancy or immunosuppressive medications.

Forty percent (22/55) of patients were admitted to the ICU, 18.2% (10/55) were treated with noninvasive ventilation, and 29.1% (16/55) required mechanical ventilation for respiratory failure. Sixteen of 22 (72.7%) ICU patients developed acute respiratory distress syndrome, and 31.3% (5/16) of those patients required support with extracorporeal membrane oxygenation. Thus far, death occurred in 5.4% (3/55) of all patients; however, 18 patients still remained hospitalized at the time of this initial report. The rate of ICU admission among hospitalized patients infected with the H1N1 virus was 39.6% (19/48), which is 50% greater than the previously reported rate of 20–25% during the 2009 pandemic influenza season (8). We are uncertain whether this high rate of ICU admission and mechanical ventilation represents a diagnosis bias or whether severity of illness being caused by the current H1N1 virus is higher. Because only the critically ill patients routinely receive bronchoscopy with bronchoalveolar lavage (BAL), it is possible that the high rate of patients who are admitted to the ICU reflects underdiagnosis of influenza in the non-ICU patient population, who may have false-negative nasopharyngeal samples.

Interestingly, of the 22 patients admitted to the ICU, 31.8% (7/22) patients had previously negative influenza tests, including 4 patients with false-negative rapid influenza antigen tests (RIDTs).

Supported by NIH grant ES013611 (J.W.H. and L.G.Q.).

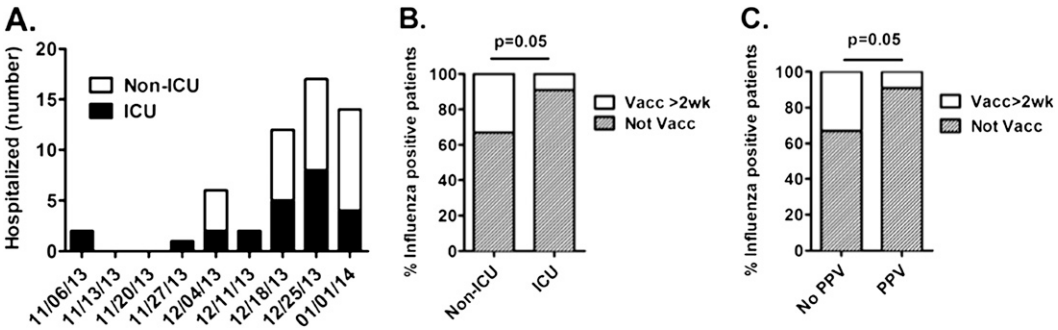


**Figure 1.** Hospitalized patients with confirmed influenza and vaccination status. (*A*) We report the number of cases of influenza at a single academic institution by week in non–intensive care unit (ICU) and ICU settings. (*B*) There was a high number of individuals that had not received the flu vaccine within 2 weeks of acute illness. There was a higher frequency of unvaccinated individuals in the ICU when compared with hospitalized non-ICU patients. (*C*) Similarly, there was a high number of individuals that had not received the flu vaccine who required positive pressure ventilation (PPV) (Optiflow [Fisher & Paykel, Auckland, New Zealand], bilevel positive airway pressure or conventional mechanical ventilation) for respiratory insufficiency, when compared with hospitalized patients who did not require ventilator support. Two-tailed Fisher exact test was used for statistical comparisons.

Although RIDTs have the advantage of quick turn-around time, their poor performance characteristics were illustrated in a metaanalysis of 159 studies, showing pooled sensitivity of 62.3% (95% CI, 57.9–66.6%) (12). The CDC recommends that antiviral treatment should not be withheld from patients with signs and symptoms suggestive of influenza infection in spite of a negative RIDT (9). Because H1N1 is known to have a high propensity for affecting the lower respiratory tract (1–3, 6, 8), BAL specimens may be more sensitive for H1N1 diagnosis than samples obtained from the upper respiratory tract (13, 14). Antivirals should not be discontinued in patients with an influenza-consistent illness until the lower tract is sampled, even if upper respiratory tract specimens are negative.

Treatment with oseltamivir was started in 81.8% (45/55) of patients in our cohort; however, delayed treatment (i.e., $\geqslant$24 h after influenza diagnosis was considered) was observed in 33.3% (15/45) of patients. Ten hospitalized patients (non-ICU) never received antiviral treatment for various reasons. The CDC recommends that the decision regarding antiviral treatment of influenza should not await laboratory confirmation and that indications for antiviral treatment include hospitalization, severe complicated and progressive illness, and presence of risk factors for influenza complications, independent of the duration of symptoms (9).

Together, our initial observations during this influenza season support a high prevalence of the H1N1 virus affecting young adults who develop severe lung injury requiring ICU care, high false-negative rates of RIDTs, and delay in starting antiviral treatment. We also note very low vaccination rates among both hospitalized and ICU patients, as well as patients requiring positive pressure ventilation. Our observations support encouraging influenza vaccination for all individuals without a contraindication, as this may prevent severe lower respiratory tract complications requiring ICU level care. ■

**Author disclosures** are available with the text of this letter at www.atsjournals.org.

**Acknowledgment:** The authors greatly appreciate the support provided by the Clinical Microbiology Laboratory at Duke University Medical Center.

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## Occupational Exposure to Vapors, Gases, Dusts, and Fumes Is Associated with Small Airways Obstruction

*To the Editor*:

Various studies have shown that occupational exposures to vapors, gases, dusts, and fumes or their composite measure (VGDF) negatively affect $FEV_1$ and the $FEV_1$/FVC ratio, indicating obstruction of predominantly the large airways (1–3). Recently we have shown that occupational exposure to pesticides is associated with substantial losses of large airway function in the general population (3). The negative effects of occupational exposures on the level of lung function were generally more pronounced in ever- than in never-smokers, suggesting that cigarette smoke–induced damage increases the susceptibility of the airways to other exposures (3). In addition to interest in large airways obstruction, there is considerable renewed interest in obstruction of the small airways, since small airways obstruction is one of the three main phenotypes of chronic obstructive pulmonary disease (COPD) (4, 5).

Supported by research school GUIDE, University of Groningen, University Medical Center Groningen (K.d.J.). The LifeLines cohort study was supported by the Dutch Ministry of Health, Welfare and Sport; the Ministry of Economic Affairs, Agriculture and Innovation; the province of Groningen; the European Union (regional development fund); the Northern Netherlands Provinces (SNN); the Netherlands Organization for Scientific Research (NWO); University Medical Center Groningen (UMCG); University of Groningen, de Nierstichting (the Dutch Kidney Foundation); and the Diabetes Fonds (the Diabetic Foundation).
Author Contributions: K.d.J. participated in the study design, analysis and interpretation of the data, and drafting of the manuscript, tables and figures. H.M.B., D.S.P., and J.M.V. obtained funding, determined the study design, participated in the analysis and interpretation of data, and critically supervised writing of the manuscript. H.K. and R.V. designed and provided the ALOHA+ JEM and participated in writing of the manuscript. All authors approved the final version of the manuscript.

Thus far, only one general population–based study in 1,735 individuals has shown associations of occupational exposure to biological dust with forced expiratory flow between 25% and 75% of FVC ($FEF_{25–75}$), an indicator of small airways obstruction (1). In addition, some small-scale studies in specific populations have shown negative effects of specific occupational exposures on the small airways, like nonasbestos mineral dusts (6), welding fumes (7, 8), and pesticide exposure (9, 10). However, these studies included individuals with large airways obstruction, or individuals with reduced FVC that may affect levels of $FEF_{25–75}$ values, and were thus not specifically investigating small airway obstruction.

We used data from 11,851 participants, 9,876 without large airways obstruction, of the LifeLines population for which we have estimated job-specific exposure to the composite measure VGDF (and separately to subcategories biological dust, mineral dust, gases, and fumes) and exposure to pesticides in general (and separately to subcategories herbicides and insecticides) as no, low, and high (0/1/2) exposure using the ALOHA+ job exposure matrix (JEM) (3). We assessed associations between occupational exposures and $FEF_{25–75}$ (ml/s) levels using linear regression with adjustment for sex, age, height, weight, current smoking, former smoking, and (log) pack-years. Because of substantial co-exposure between the specific occupational agents, we additionally adjusted the analyses on the composite measure VGDF, biological dust, mineral dust, gases, and fumes for co-exposure to pesticides, and conversely the analyses on pesticides, herbicides, and insecticides were adjusted for co-exposure to the composite measure VGDF (3).

Of the total of 11,851 subjects, 42% were male, median age being 47 years (range, 18–89 yr), 57% being ever-smokers (median number of pack-years, 10; range, 0–100). Mean $FEV_1$ % predicted was 102%, $FEV_1$/FVC 76%, and $FEF_{25–75}$ 2.9 L/s (78% predicted). Subjects without large airways obstruction ($FEV_1$/FVC $\geq$ 70%, $FEV_1$ $\geq$ 80%; n = 9,876; 83%) had a median age of 46 years (range, 18–89 yr), 40% being male and 54% being ever-smokers (median number of pack-years, 9; range, 0–84). In both groups, about 11 percent of the subjects were highly exposed to the composite measure VGDF, whereas high exposure to pesticides in general was less common (1%; Table 1).

Exposure to the composite measure VGDF, and to the subcategories biological dust and gases and fumes, was associated with lower $FEF_{25–75}$ levels (Table 1). These associations remained present when we restricted our analysis to subjects without large airways obstruction (Table 1). Moreover, findings were similar in ever- and in never-smokers (Figure 1) and when adjusted for FVC. Occupational exposure to pesticides in general and to the subcategories herbicides and insecticides tended to be associated with lower $FEF_{25–75}$ in the whole group, yet these associations largely disappeared when the analysis was restricted to subjects without large airways obstruction (Table 1).

It is known that occupational exposure to vapors, gases, dusts, and fumes affects large airway function and increases the risk for spirometry-defined COPD (1–3, 11, 12). With the present letter we add to this knowledge by showing that the small airways are affected by occupational exposure to the composite measure VGDF, and also to the subcategories biological dust, gases, and fumes. Importantly, we find these associations in subjects with normal $FEV_1$/FVC and $FEV_1$ % predicted values as well, indicating