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Post-licensure surveillance of trivalent live attenuated influenza vaccine in adults, United States, Vaccine Adverse Event Reporting System (VAERS), July 2005–June 2013

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ABSTRACT

Background: Trivalent live attenuated influenza vaccine (LAIV3) was licensed and recommended for use in 2003 in children and adults 2–49 years of age. Post-licensure safety data have been limited, particularly in adults.
Methods: We searched Vaccine Adverse Event Reporting System (VAERS) for US reports after LAIV3 from July 1, 2005–June 30, 2013 (eight influenza seasons) in adults aged ≥ 18 years old. We conducted descriptive analyses and clinically reviewed serious reports (i.e., death, life-threatening illness, hospitalization, prolonged hospitalization, or permanent disability) and reports of selected conditions of interest. We used empirical Bayesian data mining to identify adverse events (AEs) that were reported more frequently than expected. We calculated crude AE reporting rates to VAERS by influenza season.
Results: During the study period, VAERS received 1207 LAIV3 reports in adults aged 18–49 years old; 107 (8.9%) were serious, including four death reports. The most commonly reported events were expired drug administered (n = 207, 17%), headache (n = 192, 16%), and fever (n = 133, 11%). The most common diagnostic categories for non-fatal serious reports were neurological (n = 40, 39%), cardiovascular (n = 14, 14%), and other non-infectious conditions (n = 20, 19%). We noted a higher proportion of Guillain–Barré syndrome (GBS) and cardiovascular reports in the Department of Defense (DoD) population compared to the civilian population. Data mining detected disproportional reporting of ataxia (n = 15); clinical review revealed that ataxia was a component of diverse clinical entities including GBS.
Conclusions: Review of VAERS reports are reassuring, the only unexpected safety concern for LAIV3 identified was a higher than expected number of GBS reports in the DoD population, which is being investigated. Reports of administration of expired LAIV3 represent administration errors and indicate the need for education, training and screening regarding the approved indications.

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1. Introduction

In 2003, the US Food and Drug Administration (FDA) approved trivalent live attenuated influenza vaccine (LAIV3) for use in healthy non-pregnant persons aged 5–49 years old, with expansion in 2007 to include persons aged 2–49 years old [1–3]. LAIV3 is not indicated for pregnant women and persons with certain underlying medical conditions, (e.g. persons who have had severe allergic reactions to the vaccine or its components and pregnant women) [1–6]. The Advisory Committee on Immunization Practices (ACIP) includes LAIV3 as an option for influenza vaccination in approved age and risk groups [2,5–8]. In 2012, the FDA licensed quadrivalent live attenuated influenza vaccine (LAIV4), which includes the same strains in trivalent influenza vaccine plus an additional type B virus strain. LAIV4 replaced LAIV3 starting with the 2013–2014 influenza season [9–12].

Pre-licensure clinical trials [4,5,8] and post-marketing assessments using data from the Vaccine Adverse Event Reporting System (VAERS) in the first 2 years after licensure indicated an acceptable safety profile for LAIV3 in persons aged 5–49 years old [13].

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However, rare adverse events (AEs) may not be detected until a vaccine is widely used in the population [14]. A subsequent VAERS review of LAIV3 safety in children using seven additional years of data has been published [15].

We analyzed reports to VAERS following LAIV3 in persons aged 18–49 years to further assess the safety of LAIV3 in adults. In conjunction with previous assessments, the findings of this LAIV3 safety review will provide comparative data for LAIV4 safety monitoring for the 2013–14 influenza season and beyond [9–12].

2. Methods

2.1. Data source

VAERS, co-administered by the Centers for Disease Control and Prevention (CDC) and FDA, is a national spontaneous reporting system for monitoring adverse events (AEs) following vaccination [14,16]. VAERS accepts reports from vaccine manufacturers, healthcare providers, vaccine recipients and others. VAERS data include information on demographics of the person vaccinated (vaccinee), the type of vaccine(s) received and details on the AE. Signs and symptoms of AEs are coded using Medical Dictionary for Regulatory Activities (MedDRA) terms [17]. A report may be assigned one or more MedDRA preferred terms (PTs); MedDRA PTs are not medically confirmed diagnoses. A report is classified as serious, if at least one of the following is noted: death, life-threatening illness, hospitalization, prolongation of hospitalization, or permanent disability [18]. For reports categorized as serious, with the exception of reports submitted by vaccine manufacturers, medical records are routinely requested and reviewed. For the purpose of this report, "DoD population" will be used for both military personnel and DoD beneficiaries unless otherwise noted.

We analyzed US VAERS reports received by September 30, 2013 for adults aged 18–49 years vaccinated with LAIV3 from July 1, 2005–June 30, 2013 (eight influenza seasons). We also conducted a limited analysis of reports in adults aged ≥50 years old. LAIV3 is approved for individuals aged 2–49 years old so these individuals would have received LAIV3 in error or "off label." Foreign reports, duplicate reports, and reports with an unknown age were excluded. We excluded reports that stated that the live or inactivated monovalent 2009 H1N1 (pandemic H1N1) influenza vaccines were administered concomitantly with LAIV3. For serious reports, we ascertained the primary event (the event that appeared to prompt the report) and assigned a primary diagnostic category using an approach previously described [19]. Cause of death was determined based on information included in the autopsy report, death certificate, or medical record.

VAERS is a routine surveillance program conducted as a public health function and does not meet the definition of research; thus, it is not subject to Institutional Review Board review and informed consent requirements.

2.2. Descriptive analysis

We calculated descriptive statistics including mean and median age of vaccinees, the most common MedDRA PTs, and the AE onset interval (days from vaccination [day 0] until onset of first symptom(s)).

2.3. Adverse event reporting rates

We calculated crude AE reporting rates (number of LAIV3 reports per estimated LAIV3 doses administered), by influenza season in adults 18–49 years, for serious and non-serious reports. For the civilian non-institutionalized population, we estimated vaccine coverage based on the National Health Interview Survey (NHIS) for 2005–2013 [20] with US Census Bureau population estimates [21] for the 18–49 year old age group for the time period. The number of LAIV3 doses administered to the DoD population by influenza season was obtained from the Defense Medical Surveillance System (DMSS) (personal communication, Military Vaccine Agency). Therefore, the denominator for crude AE reporting rates by influenza season included estimates using NHIS and US Census Bureau data combined with direct counts from DMSS.

2.4. Clinical review of reports

We conducted clinical review of all serious reports. We also reviewed reports with the following pre-specified AEs or conditions: anaphylaxis, Guillain–Barré syndrome (GBS), Bell's palsy, and LAIV3 vaccination of individuals in whom the vaccine is not indicated (e.g., pregnant women, those with a history of asthma). We used specific MedDRA PTs to search for these pre-specified events or conditions (Appendix 1). We classified reports of anaphylaxis and GBS using the Brighton Collaboration case definitions or noted a physician diagnosis [22,23].

2.5. Disproportionality analysis

We used empirical Bayesian data mining [24] to identify AEs that were reported more frequently than expected following LAIV3, compared with other vaccines. We applied criteria published by Szarfman et al. [25].

3. Results

For the study period, VAERS received a total of 1362 LAIV3 reports in adults, of which 1207 were in individuals aged 18–49 years and 155 were in individuals aged ≥50 years (i.e., outside the 2–49 years age indication for LAIV3).

3.1. Reports in adults aged 18–49 years old

Of the 1207 reports, 562 (47%) were in males, and 107 (9%) were serious, including four reports of death. In 965 (80%) reports, LAIV3 was given without any other vaccines. The most frequently reported MedDRA PTs were expired drug administered ($n = 207$, 17%) and headache ($n = 192$, 16%); in 109 (9%) reports no AE was documented (Table 1).

3.1.1. Reporting rates

An estimated 7,316,278 LAIV3 doses were administered to civilian non-institutionalized adults aged 18–49 years and 6,904,844 doses to the DoD population (14,221,122 total doses) (Fig. 1). Crude reporting rates for serious reports decreased from 1.6 per 100,000 LAIV3 doses administered in the 2005–2006 influenza season to 0.54 per 100,000 in 2012–2013 (Fig. 2). Similarly, crude reporting rates for non-serious reports decreased from 15.6 to 4.8 per 100,000 LAIV3 doses administered. For non-serious reports we noted higher reporting rates during the 2008–2009 influenza season compared to 2006–2007 and 2010–13 seasons. The increase in reports in 2008–09 was driven by reports from DoD facilities that involved administration of expired vaccine to a large number of individuals. During 2008–2009 VAERS received 136 reports of expired drug of which 122 (90%) were from DoD.

3.1.2. Clinical review

3.1.2.1. Death reports. We identified four reports of death following LAIV3 in adults 18–49 years. A 19-year-old female died 10 days after receiving LAIV3, quadrivalent human papillomavirus, and meningococcal conjugate vaccines. Despite an extensive postmortem examination including microscopic, neuropathological,

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