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Safety evaluation of adenovirus type 4 and type 7 vaccine live, oral in military recruits

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ABSTRACT

Before the widespread adoption of vaccination, adenovirus type 4 and type 7 were long associated with respiratory illnesses among military recruits. When supplies were depleted and vaccination was suspended in 1999 for approximately a decade, respiratory illnesses due to adenovirus infections resurged. In March 2011, a new live, oral adenovirus vaccine was licensed by the US Food and Drug Administration and was first universally administered to military recruits in October 2011, leading to rapid, dramatic elimination of the disease within a few months. As part of licensure, a postmarketing study (Sentinel Surveillance Plan) was performed to detect potential safety signals within 42 days after immunization of military recruits. This study retrospectively evaluated possible adverse events related to vaccination using data from the Armed Forces Health Surveillance Branch Defense Medical Surveillance System (DMSS) database. Among 100,000 recruits who received the adenovirus vaccine, no statistically significant greater risk of prespecified medical events was observed within 42 days after vaccination when compared with a historical cohort of 100,000 unvaccinated recruits. In an initial statistical analysis of International Classification of Disease, 9th Revision, Clinical Modification codes, a statistically significant higher risk for 19 other (not prespecified) medical events occurring in 5 or more recruits was observed among vaccinated compared with unvaccinated groups. After case record data abstraction for attribution and validation, two events (psoriasis [21 vs 7 cases] and serum reactions [12 vs 4 cases]) occurred more frequently in the vaccinated cohort. A causal relation of these rare events with adenovirus vaccination could not be established given confounding factors in the DMSS, such as coadministration of other vaccines and incomplete or inaccurate medical information, for some recruits. Prospective surveillance assessing these uncommon, but potentially relevant, immune-related symptoms may be beneficial in defining potential causal association with adenovirus vaccination.

1. Introduction

Prior to the widespread use of adenovirus vaccine by the US military, adenovirus type 4 and type 7 accounted for approximately 60% of respiratory illnesses observed in hospitalized military recruits. [1,2] A live oral vaccine against adenovirus type 4 and type 7, introduced in the 1970s, was proven safe and effective, reducing adenovirus-associated respiratory illnesses by approximately 5.5-fold [1].

Despite their efficacy, production of the vaccine by the sole manufacturer was discontinued in 1996, leading to rationing of the remaining vaccine stocks until depletion in 1999 [3,4]. Surveillance during this transition period showed a resurgence in adenovirus infections coinciding with an increase in febrile respiratory illnesses among military recruits [3]. Surveillance data from 1999 to 2004 indicated a 3-fold increase in respiratory illness rates after vaccination was discontinued, and eight deaths were attributed to adenovirus-associated respiratory disease between 1999 and 2010 [4,5]. In March 2011, a new adenovirus type 4 and type 7 vaccine live, oral, was licensed by the US Food and Drug Administration (FDA), and universal vaccination was reinstated for recruits in all military branches and the Coast Guard in October 2011 [6]. Within the first two years after the vaccine's reintroduction, adenovirus-associated disease burden decreased approximately 100-fold among recruits (as reflected by a decrease from

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5.8 cases per 1000 person-weeks in 2000–2011 to 0.02 cases per 1000 person-weeks in 2012–2013) [6].

Clinical data from phase 1 and 3 studies with military recruits have demonstrated that the new vaccine is safe. In a phase 1, randomized double-blind, placebo-controlled study ($N = 58$), the most common adverse events (AEs) in the vaccinated group were nasal congestion (33%), cough (33%), sore throat (27%), headache (20%), abdominal pain (17%), arthralgia (13%), nausea (13%), and diarrhea (13%) [7]. The overall frequencies of AEs were similar to those in the placebo-treated arm [7]. In a phase 3, multicenter, randomized, double-blind, placebo-controlled study with military recruits ($N = 4040$), the incidence of AEs was comparable between vaccine and placebo arms [8]. No discontinuations due to AEs and no deaths were reported during the study [8]. Common ($\geqslant$10%) AEs associated with vaccination included upper respiratory tract infections (39%), headache (41%), nasal congestion (24%), pharyngolaryngeal pain (25%), cough (23%), arthralgia (26%), nausea (18%), abdominal pain (16%), and diarrhea (13%) [8]. Serious AEs were seen in 1% of both the vaccine and placebo arms. The most common serious AEs were psychiatric disorders and traumatic injuries.

The FDA mandated a postmarketing study (termed the Sentinel Surveillance Plan) to detect potential safety signals in military recruits exposed to this vaccine. The objective of this study was to assess the risk of medical events of interest or other events potentially related to administration of adenovirus type 4 and type 7 vaccine live, oral in a healthy US military population.

2. Methods

2.1. Study design

This study retrospectively evaluated possible AEs related to vaccination with adenovirus type 4 and type 7 vaccine live, oral using data coded based on the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) and maintained as part of the Defense Medical Surveillance System (DMSS) database. The DMSS contains longitudinal health records for US military personnel including current and historical data on diseases, medical events, vaccination, and deployment history [9]. AE data were collected for the vaccinated (hereafter referred to as exposed) cohort and a historical unvaccinated (hereafter referred to as unexposed) cohort of recruits from the previous year attending specific training sites for the Army (Fort Benning, GA; Fort Jackson, SC; Fort Leonard Wood, MO; Fort Sill, OK), Navy (Great Lakes Naval Training Center, Great Lakes, IL), Marine Corps (Parris Island, SC; San Diego, CA), and Air Force (Lackland Air Force Base, San Antonio, TX). The study was conducted under an institutional review board–granted waiver of informed consent.

2.2. Subjects

The exposed cohort consisted of healthy military recruits, 17–50 years of age, who received the live adenovirus type 4 and type 7 vaccine at the initiation of basic training at one of the specified training sites. The unexposed cohort comprised historically matched recruits who attended the same training site location during the same month in the previous year; these individuals had the same vaccine requirements as the exposed group but did not receive the adenovirus vaccine.

2.3. Routine vaccinations

Adenovirus type 4 and type 7 vaccine, live, oral contains a lyophilized formulation of selected wild-type virus, with no fewer than 32,000 tissue-culture infective doses per enteric-coated tablet. Vaccine was administered orally as two tablets (one tablet each of type 4 and type 7), swallowed whole without chewing, at the beginning of basic training. The following additional mandatory vaccines were routinely administered to military recruits without contraindications within their first week of basic training (mandatory vaccines may vary by installation): meningococcal, inactivated polio, tetanus-diphtheria-acellular pertussis, influenza (inactivated or live attenuated), pneumococcal (when indicated per Service policy), typhoid inactivated (when indicated per Service policy), and yellow fever (when indicated per Service policy). Recruits testing seronegative for measles, rubella, varicella, or hepatitis A or B were also vaccinated against these viruses. In addition, female recruits were offered the human papillomavirus vaccine per Service policy.

2.4. Data collection and extraction (Fig. 1)

Adverse medical events occurring among recruits were identified through routine health encounters and were coded by the health personnel at the training sites according to ICD-9-CM and entered into the DMSS. Reported events that occurred within 42 days following administration of adenovirus vaccine or initial mandatory vaccines during basic training were collected for each individual in the exposed and unexposed cohorts.

Adverse medical events were classified as "prespecified AEs of interest" or "cohort-associated AEs." Prespecified AEs of interest were determined by the study sponsor (including the Department of Defense) in discussion with the FDA prior to study initiation as medically important and potentially related to adenovirus vaccination (Table 1). Cohort-associated AEs were defined as any events (prespecified or otherwise) occurring at a statistically significant higher incidence rate (as determined using the Poisson regression model with two-tailed statistical testing conducted at a 5% significance level) in the exposed cohort compared with the unexposed cohort. Because of the nonspecific nature of some cohort-associated event codes at the ICM-9-CM 3-digit classification level, data were also collected at the 4- to 5-digit subcode level for all cohort-associated event codes that reached statistical significance at the 3-digit level. Cohort-associated events were captured using only data entered into the primary diagnostic code position for a particular health encounter (eg, events coded in 2nd to 8th diagnostic code positions were not considered).

The contract research organization (CRO) medical monitor conducted a medical review to determine if there was a plausible biological relationship between each potential cohort-associated ICD-9-CM event code and the vaccine. The scientific review committee (SRC) conducted an independent review and made recommendations for the inclusion of selected cohort-associated medical event codes as emergent events of interest, defined as possibly related to the adenovirus vaccination, unexpected, and clinically important.

The CRO medical monitor, in consultation with the Immunization Healthcare Branch at the Defense Health Agency further validated prespecified medical events and/or emergent events of interest by reviewing abstracted available medically relevant information from the individual records of subjects who experienced the events using a standardized data-abstraction form. During abstraction, data were captured using ICD-9-CM event codes listed in any diagnostic code position. Data (personal identifiable information redacted) abstracted from medical records included, as available, details of each report of the medical event of interest; hospital admissions related to the event; acute and chronic conditions; AEs occurring within 42 days of vaccination, excluding prespecified events of interest; alcohol, recreational drug, and tobacco use; and use of other medications and nondrug therapies. The completed abstraction forms were reviewed and approved by the Department of Defense principal investigator to ensure

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