Vaccine xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

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

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ARTICLE INFO

Article history:
Received 29 April 2016
Received in revised form 2 July 2016
Accepted 18 July 2016
Available online xxxx

Keywords:
Respiratory illness
Vaccination
Adenovirus
Retrospective
Surveillance

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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http://dx.doi.org/10.1016/j.vaccine.2016.07.033
0264-410X/

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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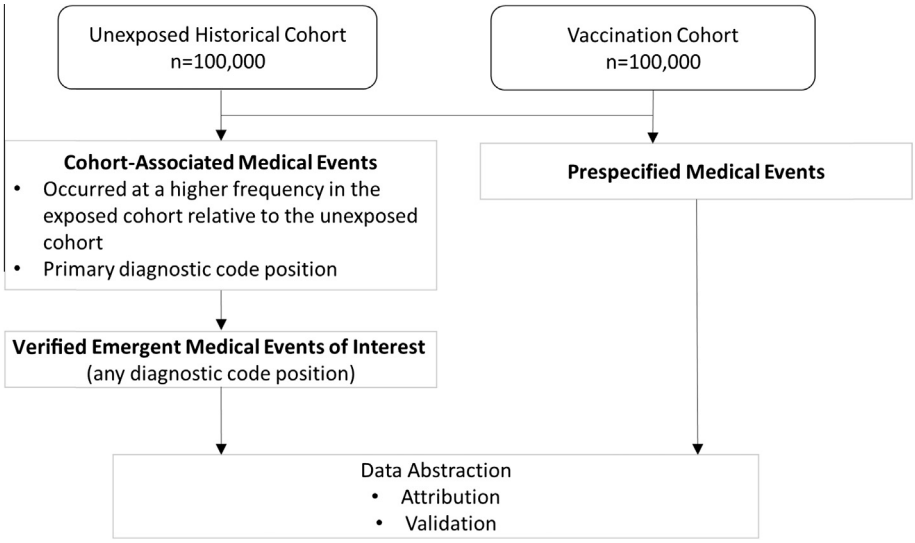

Fig. 1. Flow of information for medical event endpoints. Note: A validated event is one whose ICD-9-CM code was found in the subject's electronic health record and evidence supported the occurrence of the event.

Table 1
Prespecified medical events of interest investigated as possibly related to a live adenovirus vaccine.

ICD-9-CM code	Medical event of interest
242	Thyrotoxicosis with or without goiter
242.0	Toxic diffuse goiter
323.5	Encephalitis, immunization
323.51	Encephalitis, encephalomyelitis, immunization
345.9	Epilepsy, unspecified
357.0	Acute infective polyneuritis
420	Acute pericarditis
480	Viral pneumonia
480.0	Pneumonia due to adenovirus
486	Pneumonia, organism unspecified
518.82	Other pulmonary insufficiency, NEC
560.0	Intussusception
695.1	Erythema multiforme
780.2	Syncope and collapse
782	Symptoms involving skin and other integumentary tissue
782.1	Rash and other nonspecific skin eruption (limited to hospitalization)
977.9	Poisoning by unspecified drug or medicinal substance
995.0	Other anaphylactic shock, NEC
995.2	Other and unspecified adverse effect of drug, medicinal and biological substance (due) to correct medicinal substance properly administered
999.4	Anaphylactic shock due to serum, NEC

ICD-9-CM = International Classification of Disease, 9th Revision, Clinical Modification; NEC = not elsewhere classified.

Table 2
Demographics of cohorts at screening.

	Exposed cohort[a] n (%)	Unexposed cohort[a] n (%)
Gender		
Female	15,973 (16)	16,518 (17)
Male	84,027 (84)	83,482 (84)
Race		
White	62,879 (63)	62,530 (63)
Black	16,591 (17)	15,418 (15)
Hispanic	10,794 (11)	11,740 (12)
Asian/Pacific Islander	2913 (3)	3026 (3)
American Indian	946 (<1)	748 (<1)
Unknown/Other	5877 (6)	6538 (7)
Age at first vaccination (years)		
17	41 (<1)	60 (<1)
18	11,945 (12)	12,078 (12)
19–24	76,851 (77)	75,466 (76)
25–29	9272 (9)	9694 (10)
30–34	1643 (2)	1861 (2)
35–39	229 (<1)	676 (<1)
40–50	19 (<1)	165 (<1)
Branch of service		
Air Force	21,813 (22)	21,813 (22)
Army	40,538 (41)	40,538 (41)
Marine Corps	19,662 (20)	19,662 (20)
Navy	17,987 (18)	17,987 (18)

[a] Exposed and unexposed cohort each has a total of 100,000 recruits.

completeness, to the extent possible, and appropriateness of the abstracted data before release. For certain codes where large numbers of events were reported, a random sample of the corresponding records was abstracted per recommendation by the SRC. Following abstraction, some events were rejected as related to vaccination for any of the following reasons: (1) the event occurred outside of the relevant exposure window; (2) confirmed laboratory findings indicated that the medical event occurred prior to vaccination; (3) the event was due to a preexisting condition without evidence of an acute event related to vaccination; and, (4) there was a lack of documentation for a clinical syndrome or expected treatment consistent with the event term.

2.5. Statistical methods

The final cumulative analysis was planned and performed after 100,000 matched recruits had accrued in the exposed cohort. A sample size of 200,000 (100,000 per cohort) was expected to provide more than 80% power to detect a 2-fold increase in prevalence, assuming an event was present in at least 0.024% of the unexposed cohort, and a two-sided alpha of 0.05.

Analyses of prespecified and emergent medical events of interest were conducted by calculating the incidence rate for each cohort and determining the risk ratio. Incidence rate was defined as the total number of subjects experiencing a specific event code for the first time during the study period divided by person-years at risk among recruits over the same period. Person-years were estimated using the number of recruits and 42 days following

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Table 3
Incidence rates, risk ratios, and 95% confidence interval for prespecified medical events of interest among healthy military recruits vaccinated with adenovirus type 4 and type 7 vaccine.

ICD-9-CM code	Description	Exposed cohort n (IR/100,000 P-Y)	Unexposed cohort n (IR/100,000 P-Y)	RR	95% CI
	Total number of prespecified events	3474	4789	0.7254	0.69–0.76
242	Thyrotoxicosis	11 (95.66)	10 (86.96)	1.10	0.47–2.59
242.0	Toxic diffuse goiter	0	0	–	–
323.5	**Encephalitis, immunization**	**1 (8.70)**	**1 (8.70)**	**1.00**	**0.06–15.99**
323.51	**Encephalitis, encephalomyelitis, immunization**	**0**	**0**	**–**	**–**
345.9	Epilepsy	18 (156.54)	35 (304.37)	0.51	0.29–0.91
357.0	**Acute infective polyneuritis**	**3 (26.09)**	**7 (60.87)**	**0.43**	**0.11–1.66**
420	**Acute pericarditis**	**2 (17.39)**	**3 (26.09)**	**0.67**	**0.11–3.99**
480.0	Pneumonia, adenovirus	0	10 (86.96)	–	–
480	Viral pneumonia	0	24 (208.71)	–	–
486	Pneumonia, unspecified	1432 (12453.26)	2648 (23028.09)	0.54	0.51–0.58
518.82	Other pulmonary insufficiency	3 (26.09)	4 (34.79)	0.75	0.17–3.35
560.0	**Intussusception**	**1 (8.70)**	**1 (8.70)**	**1.00**	**0.06–15.99**
695.1	Erythema multiforme	0	0	–	–
780.2	Syncope	394 (3426.38)	454 (3948.17)	0.87	0.76–0.99
782	Symptoms involving skin	1459 (12688.06)	1437 (12496.74)	1.02	0.94–1.09
782.1	Rash inpatient	2 (17.39)	10 (86.96)	0.20	0.04–0.91
977.9	**Poisoning, unspecified**	**6 (52.18)**	**3 (26.09)**	**2.00**	**0.50–8.00**
995.0	**Anaphylactic shock, other**	**46 (400.03)**	**29 (252.20)**	**1.59**	**1.00–2.52**
995.2	Adverse effect of drug, unspecified	96 (834.86)	110 (956.60)	0.87	0.66–1.15
999.4	Anaphylactic shock, serum	0	3 (26.09)	–	–

CI = confidence interval; ICD-9-CM = International Classification of Disease, 9th Revision, Clinical Modification.
Incidence rate (IR) per 100,000 person-years (P-Y) of exposure (IR/100,000 P-Y) = event * 100,000/P-Y of exposure; risk ratio (RR) = IR exposed/IR unexposed.
Event codes listed in **bold** were selected for abstraction investigation as emergent events of interest.

vaccination (0.1150 years) as the period. The risk ratio was defined as the ratio of the exposed versus unexposed incidence rates. Cohort-associated events were identified using a Poisson regression model with two-tailed statistical testing conducted at a 5% significance level.

3. Results

3.1. Study subjects

Adenovirus vaccination was begun on October 24, 2011, and the final exposed recruit was vaccinated on October 5, 2012. Data from a total of 200,000 recruits (100,000 in each cohort) were evaluated for this study, with an estimated 11,499 person-years for each cohort.

The demographic characteristics were similar for the exposed and unexposed cohorts, indicating that the two groups were comparable (Table 2). In both groups, 84% of subjects were male; distribution by race/ethnicity was also similar between the exposed and unexposed cohorts. Ages at first vaccination ranged from 17 to 50 years. The Army accounted for the greatest proportion of study subjects in each cohort, followed by the Air Force, the Marine Corps, and the Navy.

3.2. Prespecified medical events of interest

A total of 3474 and 4789 prespecified medical events of interest (including ICD-9-CM event codes listed in any diagnostic code position) were experienced by the exposed and unexposed cohorts, respectively (Table 3). None of the prespecified medical events was found to be statistically more frequent in the exposed group, compared to the unexposed group. A significant reduction in risk was observed in the vaccinated cohort for epilepsy, pneumonia (organism unspecified), syncope and collapse, and rash and other nonspecific skin eruption (limited to hospitalization). According to protocol, however, these cases were not verified by abstraction because of the reduced risk associated with these events. The reduction in risk could not be calculated for viral pneumonia, pneumonia due to adenovirus, or anaphylactic shock due to serum, because no cases were reported in the exposed cohort.

A total of 103 patient cases were abstracted, including 59 in the exposed cohort and 44 in the unexposed (Table 4). In addition, despite the lack of statistically significant findings, medical records for seven codes of rare and/or serious events were recommended for abstraction. Abstraction of these seven events identified four that were possibly related to adenovirus vaccination: 323.52 (myelitis, $n = 1$), 420.9 (pericarditis, $n = 1$), 357.0 (acute infective polyneuritis, $n = 2$), and 995.0 (other anaphylactic shock, not elsewhere classified,

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Table 4
Sampling strategy and number of completed abstractions for prespecified and emergent medical events of interest.

ICD-9-CM code	Description	Sampling Strategy	Exposed Cohort			Unexposed Cohort	
			Number of Completed Abstractions	Number Validated	Number Possibly Related	Number of Completed Abstractions	Number Validated
Prespecified medical events of interest							
323.5	Encephalitis, immunization	All	1	1	1	1	0
323.51	Encephalitis, encephalomyelitis, immunization	All	0	0	0	0	0
357.0	Acute infective polyneuritis	All	3	2	2	7	6
420.9	Acute pericarditis	All	2	1	1	3	0
560.0	Intussusception	All	1	0	0	1	1
977.9	Poisoning, unspecified	All	6	6	0	3	3
995.0	Anaphylactic shock, other	All	46	42	3	29	23
Emergent events of interest							
070.30	Viral hepatitis B	All exposed	20	20	0	n/a	n/a
282.2	Anemias due to disorders of glutathione	10% random sample of Lackland cases	41	2	0	18	0
282.5	Sickle cell trait	10% random sample of Lackland cases	25	25	0	9	9
285.9	Anemia, unspecified	10% random sample of Great Lakes cases	21	11	0	5	1
447.6	Arteritis, unspecified	All	43	0	0	14	0
696.1	Other psoriasis	All	22	21	8	9	7
999	Complications of medical care, NEC	All	51	12	13[a]	16	4

ICD-9-CM = International Classification of Disease, 9th Revision, Clinical Modification; n/a = not available; NEC = not elsewhere classified.
[a] Includes 5 events validated by medical review.

$n = 3$); however, in all instances, other vaccines were coadministered and could not be ruled out as having contributed to the events. The data from the abstractions did not indicate any definitive biological or clinical associations with adenovirus vaccination.

3.3. Cohort-associated medical events

There were 19 cohort-associated medical events with statistically significant higher risk ratios in the exposed cohort versus the unexposed cohort described at the 3-digit ICD-9-CM code level and the 4- and 5-digit subcode levels (Table 5). Based on SRC review of the data and medical evaluations, seven cohort-associated events were selected as emergent events of interest for further investigation and abstraction (Table 6).

3.4. Emergent events of interest

A total of 1624 and 974 emergent events of interest in seven codes were experienced by the exposed and unexposed cohorts, respectively. Most events were recorded at Lackland Air Force Base and Great Lakes Naval Training Center. Medical information related to these events from 292 subjects was abstracted for validation including 221 from the exposed cohort and 71 from the unexposed cohort. In the case of three ICD-9-CM events that

Table 5
Risk ratios for statistically significant 4- and 5-digit subcodes of cohort-associated medical events among healthy military recruits vaccinated with adenovirus type 4 and type 7 vaccine.

ICD-9-CM code	Description	RR (95% CI)
070.30	**Viral hepatitis B without hepatic coma acute or unspecified without hepatitis delta**	**4.00 (1.50–10.66)**
133.0	Scabies	1.92 (1.37–2.70)
282.2	**Anemias due to disorders of glutathione metabolism**	**1.77 (1.53–2.04)**
282.5	**Sickle-cell trait**	**1.82 (1.53–2.16)**
285.9	**Anemia unspecified**	**2.03 (1.68–2.45)**
300.9	Unspecified nonpsychotic mental disorder	1.45 (1.09–1.94)
301.9	Unspecified personality disorder	1.95 (1.17–3.27)
310.2	Postconcussion syndrome	2.56 (1.18–5.52)
380.4	Impacted cerumen	1.34 (1.10–1.63)
447.6	**Arteritis unspecified**	**3.07 (1.68–5.62)**
472.0	Chronic rhinitis	1.27 (1.04–1.55)
564.00	Unspecified constipation	1.24 (1.12–1.37)
564.01	Slow transit constipation	3.20 (1.17–8.74)
565.0	Anal fissure	1.58 (1.04–2.40)
696.1	**Other psoriasis and similar disorders**	**2.44 (1.13–5.31)**
704.8	Other specified diseases of hair and hair follicles	1.65 (1.55–1.76)
706.1	Other acne	1.38 (1.18–1.63)
737.30	Scoliosis (and kyphoscoliosis) idiopathic	1.58 (1.15–2.19)
739.2	Nonallopathic lesions of thoracic region, NEC	2.38 (1.04–5.43)

CI = confidence interval; ICD-9-CM = International Classification of Disease, 9th Revision, Clinical Modification; NEC = not elsewhere classified; RR = risk ratio.
Event codes listed in **bold** were selected for investigation as emergent events of interest.

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Table 6
Incidence rates, risk ratios, and 95% confidence intervals for emergent medical events of interest among healthy military recruits vaccinated with adenovirus type 4 and type 7 vaccine.

ICD-9-CM code	Description	Military branch	Exposed cohort n (IR/100,000 P-Y)	Unexposed cohort n (IR/100,000 P-Y)	RR	95% CI
070.30	Viral hepatitis B	Overall	21 (182.62)	6 (52.18)	3.50	1.41–8.67
		Air Force	0	1 (39.86)	–	–
		Army	0	0	–	–
		Marine Corps	5 (221.15)	3 (132.69)	1.67	0.40–6.97
		Navy	16 (773.57)	2 (96.70)	8.00	1.84–34.79
282.2	Anemias due to disorders of glutathione metabolism	Overall	540 (4696.07)	308 (2678.50)	1.75	1.52–2.02
		Air Force	413 (16465.53)	176 (7016.79)	2.35	1.97–2.80
		Army	1 (21.45)	0	–	–
		Marine Corps	96 (4246.04)	98 (4334.50)	0.98	0.74–1.30
		Navy	30 (1450.45)	34 (1643.85)	0.88	0.54–1.44
282.5	Sickle cell trait	Overall	384 (3339.43)	218 (1895.82)	1.76	1.49–2.08
		Air Force	267 (10644.78)	103 (4106.41)	2.59	2.07–3.25
		Army	1 (21.45)	0	–	–
		Marine Corps	76 (3361.45)	87 (3847.98)	0.87	0.64–1.19
		Navy	40 (1933.94)	28 (1353.76)	1.43	0.88–2.32
285.9	Anemia, unspecified	Overall	539 (4687.38)	391 (3400.30)	1.38	1.21–1.57
		Air Force	70 (2790.77)	59 (2352.22)	1.19	0.84–1.68
		Army	171 (3668.38)	198 (4247.60)	0.86	0.70–1.06
		Marine Corps	33 (1459.58)	53 (2344.17)	0.62	0.40–0.96
		Navy	265 (12812.33)	81 (3916.22)	3.27	2.55–4.20
447.6	Arteritis, unspecified	Overall	47 (408.73)	17 (147.84)	2.76	1.59–4.81
		Air Force	4 (159.47)	0	–	–
		Army	0	1 (21.45)	–	–
		Marine Corps	38 (1680.73)	15 (663.44)	2.53	1.39–4.61
		Navy	5 (241.74)	1 (48.35)	5.00	0.58–42.80
696.1	Other psoriasis	Overall	32 (278.29)	13 (113.05)	2.46	1.29–4.69
		Air Force	4 (159.47)	1 (39.87)	4.00	0.45–35.79
		Army	13 (278.88)	7 (150.17)	1.86	0.74–4.65
		Marine Corps	7 (309.61)	1 (44.23)	7.00	0.86–56.90
		Navy	8 (386.79)	4 (193.39)	2.00	0.60–6.64
999	Complications of medical care, NEC	Overall	61 (530.48)	21 (182.63)	2.90	1.77–4.77
		Air Force	20 (797.36)	4 (159.47)	5.00	1.71–14.63
		Army	15 (321.79)	8 (171.62)	1.88	0.80–4.42
		Marine Corps	3 (132.69)	3 (132.69)	1.00	0.20–4.95
		Navy	23 (1112.01)	6 (290.09)	3.83	1.56–9.41

CI = confidence interval; ICD-9-CM = International Classification of Disease, 9th Revision, Clinical Modification; NEC = not elsewhere classified.
Incidence rate (IR) per 100,000 person-years (P-Y) of exposure (IR/100,000 P-Y) = event * 100,000/P-Y of exposure; risk ratio (RR) = IR exposed/IR unexposed.

occurred predominantly at a single base, abstraction of a 10% random sampling of code 282.2 (anemias due to disorders of glutathione), 282.5 (sickle cell trait), and 285.9 (anemia unspecified) was performed on subjects from the Lackland Air Force Base and Great Lakes Naval Training Center (see Table 6 for events by base). A summary of the cases validated and considered related is presented in Table 4**.** Among the validated events, two event codes (696.1 [other psoriasis] and 999 [complications of medical care, not elsewhere classified]) were found to be possibly related to adenovirus vaccination. Among the 21 validated cases with code 696.1 in the exposed cohort, eight were assessed as possibly related to vaccination. Among the 13 cases with code 999 and assessed as related in the exposed cohort, five were validated; these included four cases with subcode 999.52 (other serum reaction due to vaccination) and one with subcode 999.59 (other serum reaction). The coding for the eight remaining cases was not supported by event details and was not validated. No definitive biological or clinical association was established between the data from the abstractions and adenovirus vaccination.

4. Discussion and conclusion

A statistically significant higher risk for 19 medical event codes was detected in the DMSS database among recruits who received the adenovirus type 4 and type 7 vaccine (exposed) compared with unvaccinated (unexposed) recruits. None of the prespecified medical event codes was found to be statistically more frequent in the exposed cohort than in the unexposed cohort, although anaphylactic shock (code 995.0) approached significance (risk ratio = 1.59, 95% confidence interval 1.00–2.52). For most of the cohort-associated events, the SRC determined that there was no biologically plausible explanation for the increased frequency in the vaccinated cohort. In general, these events were associated with factors related to demography (eg, preponderance of an event by gender or race) and/or geography (eg, concentration of an event at a particular military base). However, seven events were considered emergent events of interest and six were validated through abstraction of medical records. Of the six validated events, only two (696.1-psoriasis and 999.5-serum reactions) had events that were considered possibly related to vaccination. Despite the statistically significant association between these event codes and vaccine exposure, the true relationship between the occurrence of the event and administration of the adenovirus vaccine cannot be evaluated based on the statistical results alone.

The retrospective nature of this study limits interpretation of the relationship between the adenovirus vaccine and the few events that occurred during the 42-day postvaccination period. The military recruit population, by its nature, limits the impact of confounding variables such as age and health status. Variability of reporting and differences in the experience and training of

Please cite this article in press as: Choudhry A et al. Safety evaluation of adenovirus type 4 and type 7 vaccine live, oral in military recruits. Vaccine (2016), http://dx.doi.org/10.1016/j.vaccine.2016.07.033

medical personnel at the basic training sites, as well as limitations of the DMSS database such as loss to follow-up due to discharge from the military, reduce the ability to distinguish a genuine safety signal associated with the adenovirus vaccine from other contributing factors.

For these reasons, the potential causes of the observed increases in psoriasis, anaphylaxis, and other hypersensitivity reactions are unclear. Prospective surveillance assessing these uncommon, but potentially relevant, immune-related symptoms may be beneficial in defining potential causal association with adenovirus vaccination.

It should be highlighted that, subsequent to the institution of adenovirus vaccination and conduct of this study, US military investigators have also noted a reduction in adenovirus-associated respiratory illnesses; these findings are consistent with the beneficial effects described in earlier reports [1,3,4,6].

Disclosure statement

All authors have approved the final manuscript. AC and JM report employment by Teva Pharmaceuticals, Inc., outside the submitted work; JDA reports employment by INC Research LLC, the contract research organization who managed the study on behalf of Teva Pharmaceuticals, Inc. MY and LC have nothing to disclose.

Acknowledgments

The authors thank the following for their contributions to this manuscript: Andrew Towle, PhD, of AVP Biologics LLC; Carrie Yon, of Teva Pharmaceuticals; Traci Vactor, BS, Immunization Healthcare Branch, Defense Health Agency; and Hayley Hughes, DrPH, MPH, CSP, of Workforce Health and Medical Support Division, US Department of Homeland Security, Office of Health. We also gratefully acknowledge the assistance of Angelia A. Eick-Cost, PhD, ScM, Armed Forces Health Surveillance Branch, Public Health Division, Defense Health Agency, for provision of recruit demographic and diagnostic outcome data. The study was managed by Angie Graves, MBA, of INC Research LLC. The study was supported by contract DAMD17-01-C-0058 from the US Department of Defense to Teva Branded Pharmaceutical Products R&D. Financial support for medical writing assistance from Ada Ao-Baslock, PhD, of Powered 4 Significance LLC was provided by Teva Branded Pharmaceutical Products R&D.

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