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Adverse events following adenovirus type 4 and type 7 vaccine, live, oral in the Vaccine Adverse Event Reporting System (VAERS), United States, October 2011–July 2018

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ABSTRACT

Background: In March 2011, the U.S. Food and Drug Administration licensed adenovirus type 4 and type 7 vaccine, live, oral (Barr Labs, Inc.) (adenovirus vaccine) for use in military personnel 17 through 50 years of age. The vaccine was first universally administered to U.S. military recruits in October 2011. We investigated adverse event (AE) reports following the adenovirus vaccine submitted to the Vaccine Adverse Event Reporting System (VAERS).

Methods: We searched the VAERS database for U.S. reports among persons who received adenovirus vaccine during October 2011 through July 2018 including participants in a military observational study. We reviewed all serious reports and accompanying medical records. We compared the proportion of serious reports in a proxy military recruit population and reviewed all reports of suspected allergic reactions following adenovirus vaccination.

Results: During the analytic period, VAERS received 100 reports following adenovirus vaccination; 39 (39%) were classified as serious and of these, 17 (44%) were from the observational study. One death was reported. Males accounted for 72% of reports. Median age of vaccinees was 19 years (range 17–32). The most frequently reported serious AEs were Guillain Barré syndrome (GBS) (n = 12) and anaphylaxis (n = 8); of these, two GBS and all the anaphylaxis reports were reported in the observational study. Reports documented concurrent receipt of multiple other vaccines (95%) and penicillin G (IM Pen G) or other antibiotics (50%).

Conclusions: The reporting rate for serious AEs was higher than with other vaccines administered in the comparison military recruit population (39% vs 18%); however, we identified no unexpected or concerning pattern of adenovirus vaccine AEs. Co-administration of vaccines and IM Pen G was commonly reported in this military population. These exposures may have contributed to the GBS and anaphylaxis outcomes observed with the adenovirus vaccine. Future adenovirus vaccine safety studies in a population without these co-administrations would be helpful in clarifying the vaccine's safety profile.

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1. Introduction

Human adenoviruses were first described in the 1950s and are associated with a broad spectrum of clinical illnesses, including febrile upper respiratory disease, pneumonia, gastrointestinal disease and conjunctivitis [1]. Mild or subclinical illness is common and by the age of 10 years, most children have serologic evidence of exposure to one or more serotypes [2]. Different adenovirus serotypes are associated with different disease syndromes. Severe illness can occur in newborn or elderly patients or in patients with underlying medical conditions but is usually rare in otherwise healthy adults [3]. Exceptions are outbreaks of acute febrile respiratory disease that have occurred among military recruits predominantly caused by adenovirus type 4 and type 7 [4–6].

Beginning in the 1970s, a safe and effective, live, oral vaccine against adenovirus type 4 and type 7 was routinely administered

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to new military recruits for the prevention of adenovirus-associated respiratory illnesses [7–9]. In 1996, the manufacturer ceased production of the vaccine, although some administration continued until all the vaccine stock was finally depleted in 1999. Surveillance data from 1999 to 2004 indicated a 3-fold increase in the rate of respiratory illness among military recruits, and a total of eight deaths in recruits were attributed to adenovirus-associated respiratory disease between 1999 and 2010 [10–12].

Soon after, pre-licensure development of a new adenovirus type 4 and type 7 vaccine, live, oral was begun. Safety studies included a phase 1, randomized, double-blind placebo-controlled study (n = 58) wherein the most common adverse events (AEs) reported included nasal congestion (33%), cough (33%), sore throat (27%), headache (20%), abdominal pain (17%), arthralgia (13%), nausea (13%), and diarrhea (13%). These overall frequencies of AEs were similar to those in the placebo-treated subjects [13].

Similarly, in a phase 3 multicenter randomized double-blind, placebo-controlled study with military recruits (n = 4040), the incidence of AEs was comparable between the vaccine and placebo arms [14]. No discontinuations due to AEs, and no deaths were reported during the study [14]. Common (≥10%) AEs reported as associated with vaccination included upper respiratory tract infections (39%), headache (41%), nasal congestion (24%), pharyngeal pain (25%), cough (23%), arthralgia (26%), nausea (18%), abdominal pain (16%), and diarrhea (13%). Serious AEs were seen in 1% of both the vaccine and placebo arms. The most common serious AEs were psychiatric disorders and traumatic injuries.

In March 2011, the new adenovirus type 4 and type 7 vaccine, live, oral (Barr Labs, Inc.) (adenovirus vaccine) was licensed by the U.S. Food and Drug Administration (FDA), and in October of that year, universal vaccination for military recruits was re-implemented [15,16]. Within the first 2 years following the vaccine's introduction, the burden of adenovirus-associated disease among recruits dramatically decreased (i.e., from 5.8 cases per 1000 person-weeks in 2000–2011 to 0.02 cases per 1000 person-weeks in 2012–2013) [16].

From 2011 to 2012, an FDA-mandated, post marketing military observational study (termed the Sentinel Surveillance Plan) was conducted using the Department of Defense's (DoD) Defense Medical Surveillance System (DMSS) database [17]. This study compared 100,000 recruits exposed to the adenovirus vaccine with a historical unexposed cohort and identified statistical signals for psoriasis, anaphylaxis and other hypersensitivity reactions as emergent AEs possibly related to vaccination [18]. However, due to limitations inherent in this retrospective database evaluation, including co-administration of other vaccines, it was unclear whether these AEs were causally related to adenovirus vaccination [18].

We evaluated the safety profile of the adenovirus vaccine by reviewing reports submitted to the Vaccine Adverse Event Reporting System (VAERS).

2. Methods

2.1. Vaccine Adverse Events Reporting System (VAERS)

VAERS, established in 1990, is a national passive surveillance system, co-administered by the Centers for Disease Control and Prevention (CDC) and FDA that receives reports of AEs following vaccination [19]. Anyone, including healthcare providers, vaccine recipients, vaccine manufacturers, and other reporters can report an AE. Reports are submitted voluntarily either directly from individual reporters, who may be reporting for themselves or others, or secondarily from vaccine manufacturers, who also receive reports, and in turn, submit them to VAERS. Reporting is encouraged for any clinically important or unexpected AE, even if the reporter is not sure if a vaccine caused the event [19]. VAERS accepts all reports without rendering judgment on the clinical importance or whether vaccine(s) might have caused the AE. The VAERS report form collects information on age, sex, vaccine(s) administered, AE (s) experienced, medical conditions at the time of vaccination, and medical history. There is also a separate box on the form to provide data on concurrent medications, although this information may not be included by the reporter. The VAERS form also collects whether the vaccination was at a military clinic or hospital and if the vaccine was purchased with military funds. Signs and symptoms of AEs are coded by trained personnel using the Medical Dictionary for Regulatory Activities (MedDRA), a clinically validated, internationally standardized medical terminology [20]. A VAERS report may be assigned one or more MedDRA preferred terms (PT). A PT is a distinct descriptor for a symptom, sign, disease, diagnosis, therapeutic indication, investigation, surgical or medical procedure, and medical, social, or family history characteristic [21]. MedDRA PTs are not confirmed diagnoses. Reports are classified as serious based on the Code of Federal Regulations if one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization, permanent disability, or congenital anomaly [22]. For serious reports from sources other than vaccine manufacturers, medical records are routinely requested and made available to VAERS personnel. Reports of medication errors (e.g., vaccine administered to patient of inappropriate age) may also be reported and are assigned MedDRA PTs, even if there is no AE *per se*.

We analyzed U.S. VAERS reports for the analytic period October 1, 2011 through July 31, 2018. We excluded non-U.S. reports and duplicate reports. We identified separately those reports filed from the military observation study (the Sentinel Surveillance Plan study) which enrolled recruits vaccinated during October 24, 2011 through October 5, 2012. For comparison, we analyzed reports received by VAERS involving military service members that did not involve adenovirus vaccine (i.e., reports involving other vaccines). Since the VAERS form does not specifically identify recruits in the military population, we identified a proxy military recruit comparison group i.e., military reports to VAERS with a date of vaccination from July 1, 1999 through October 31, 2011 (which corresponds to the period when adenovirus vaccine was unavailable in the military population) in service personnel aged 17–24 years old and from the eight states which have DoD initial entry recruit sites and one US Coast Guard site. The sites are as follows: Army: Ft. Jackson, SC; Ft. Sill, OK; Ft. Leonard Wood, MO; Ft. Benning, GA, Marine Corps: San Diego CA Recruit Depot, Parris Island NC Marine Recruit Depot; Air Force: Lackland AFB Recruit Site, TX; Navy: Great Lakes Recruit Site, IL; US Coast Guard: Cape May Recruit Site, NJ. Because VAERS is a routine surveillance program conducted for public health, it does not meet the definition of research and is not subject to Institutional Review Board approval and informed consent requirements.

2.2. Clinical review of reports

All reports were reviewed and when vaccination records were available, we confirmed that adenovirus vaccine was administered. Two physicians (MMM and IPS) independently reviewed each report and accompanying medical records when available to confirm adenovirus vaccination and to confirm the diagnosis when possible. The main diagnosis for each report was categorized into a MedDRA System Organ Class (SOC) grouping. Reports suggestive of anaphylaxis or GBS were further classified using the Brighton Collaboration criteria or a physician's diagnosis [23,24]. We also

reviewed all reports of suspected allergic reactions identified as having the MedDRA SOC immune system disorders.

3. Results

3.1. Descriptive analysis

During the study period, VAERS received a total of 100 reports following adenovirus vaccine; all reports indicated the source as the U.S military (Table 1). As of April 2018, over 1.3 million doses of adenovirus had been administered, for a rate of approximately 7.7 reports per 100,000 doses administered. Among all reports, the earliest vaccination date with the adenovirus vaccine we identified was November 9, 2011. Twenty nine (29%) reports were filed from the military observational study. Males accounted for 72 (72%) reports (over 80% of U.S. military recruits are male). The median age of patients in reports was 19 years (range 17–32 years). In only five reports, the adenovirus vaccine was given alone, and one of these was a serious report of Guillain Barré syndrome. However, the patient had received five additional vaccines in the 4 weeks prior to adenovirus vaccine, including seasonal influenza vaccine. In the remaining 95 reports, patients received between two and eight concomitant vaccines and should have also received routine prophylactic intramuscular penicillin G (or other antibiotic if allergic to penicillin) according to standard DoD protocol. Our VAERS review found in 48 of 50 reports that documented concurrent administration of an antibiotic, it was reported as penicillin G.

Thirty-nine reports were identified as serious (of these 17 [44%] were in the military observational study) with the following conditions, based on automated MedDRA coding terms assigned to the report: Guillain Barré syndrome (n = 12), anaphylaxis (n = 8), and death (n = 1). The main diagnosis for each report was categorized into a MedDRA SOC grouping. The remaining 18 serious non-death reports included various diagnoses which were classified using MedDRA SOC as nervous system disorders (n = 5; including Hereditary Neuropathy with Predisposition to Pressure Palsy (HNPP) [n = 2] [25], epilepsy [n = 2], and acute disseminated encephalomyelitis (ADEM) [n = 1]), immune system disorders (n = 2; including hypersensitivity Type III [n = 1] and scleroderma [n = 1]), and a category for Other SOC (n = 11; including injury and poisoning and procedural complications [n = 4] and single reports each for infections and infestations, blood and lymphatic system disorders, musculoskeletal and connective tissue disorders, cardiac disorders, renal and urinary disorders, gastrointestinal disorders and psychiatric disorders) (Table 2). One additional report with HNPP was classified as a non-serious report and is described below.

The most frequent MedDRA PT codes for serious (n = 39) and non-serious (n = 61) adenovirus vaccine reports (excluding laboratory or test result codes) are shown in Table 3. Among the serious reports, in addition to PTs for GBS and anaphylaxis were several PTs specific for neurologic and musculoskeletal symptoms commonly associated with a GBS diagnosis. Among the non-serious reports, in addition to the specific anaphylaxis PT were several other PTs for signs and symptoms associated with anaphylaxis and allergic reactions.

Table 1
Characteristics of Adenovirus Type 4 and Type 7 Vaccine, Live, Oral reports in U.S. military personnel to VAERS, October 2011 through July 2018.

Report characteristics	Military No. (%)	Military observational study[5] No. (%)	Total No. (%)
Total Reports	71	29	100
Serious[1,2]	22 (31)	17 (58.6)	39 (39)
Male	50 (70.4)	22 (75.9)	72 (72)
Median onset interval (range) days	0 (0–366)	5 (0–367)	1 (0–367)
Adenovirus vaccine given alone[3]	4 (5.6)	1 (3.4)	5 (5)
Median age (range) years	19 (17–32)	19.5 (18–27)	19 (17–32)
Age groups years[4]			
17–19	37 (52.1)	2 (6.9)	39 (39)
20–29	32 (45.1)	2 (6.9)	34 (34)
≥30	2 (2.8)	0	2 (2)
Unknown age	0	25 (86.2)	25 (25)

[1] Includes death, life-threatening illness, hospitalization or prolongation of existing hospitalization, or permanent disability.
[2] One of the serious reports was a death.
[3] Other most commonly given concomitant vaccines included: Meningococcal conj. in 78 (78%), seasonal influenza in 74 (74%), Tdap in 68 (68%), Hepatitis A/B combined in 26 (26%). Hepatitis B in 20 (20%).
[4] Age not reported in 25 (25%) reports.
[5] Sentinel Surveillance Plan-FDA-mandated post-marketing study.

Table 2
Diagnostic categories of non-death serious reports following Adenovirus Type 4 and Type 7 Vaccine, Live, Oral reports in U.S. military personnel to VAERS, October 2011 through July 2018.

Diagnostic category	Military (N = 21) N (%)	Military observational study[4] (N = 17) N (%)	Total (N = 38) N (%)
Nervous system disorders	14 (66.7)	3 (17.6)	17 (44.7)
Guillain Barré syndrome	10	2	12
HNPP[1]	2	0	2
Epilepsy	1	1	2
ADEM[2]	1	0	1
Immune system disorders	2 (9.5)	8 (47.1)	10 (26.3)
Anaphylactic shock	0	8	8
Hypersensitivity Type III reaction	1	0	1
Scleroderma	1	0	1
Injury and poisoning and procedural complications[3]	0	4 (23.5)	4 (10.5)
Infections and Infestations	1 (4.8)	0	1 (2.6)
Blood and lymphatic disorders	1 (4.8)	0	1 (2.6)
Musculoskeletal and connective tissue disorders	1 (4.8)	0	1 (2.6)
Cardiac disorders	0	1 (5.9)	1 (2.6)
Renal and urinary disorders	1(4.8)	0	1 (2.6)
Gastrointestinal disorders	0	1 (5.9)	1 (2.6)
Psychiatric disorders	1 (4.8)	0	1 (2.6)

[1] HNPP = Hereditary Neuropathy with Liability to Pressure Palsy.
[2] ADEM = acute disseminated encephalomyelitis.
[3] Implicated medications: penicillin G and ibuprofen, pseudoephedrine, acetaminophen for nonspecific symptoms.
[4] Sentinel Surveillance Plan-FDA-mandated post-marketing study.

3.2. Pre-specified conditions

3.2.1. Death report

We identified one report of a death following adenovirus vaccine. A 19-year-old female received concurrently: adenovirus, hepatitis A, seasonal influenza, meningococcal conjugate and Tdap vaccines. One day later, she presented to the Emergency Department (ED) with complaints of nausea, vomiting, abdominal pain and distension; a chest radiograph revealed a left lung infiltrate and she was discharged on clarithromycin therapy. She returned to the ED with fever, dizziness, shortness of breath, cough and repeat chest radiograph demonstrated bilateral pulmonary infiltrates. She suffered a respiratory arrest, was intubated and placed on mechanical ventilation in ICU; however, her condition rapidly

Table 3
Most commonly reported adverse events[1] following Adenovirus Type 4 and Type 7 Vaccine, Live, Oral in VAERS, October 2011-July 2018[2].

Adverse event[2] (all adenovirus vaccine reports)	N (%)
Among Non-serious[3] Reports	N = 61
Pruritus	10 (16.4)
Rash	10 (16.4)
Urticaria	10 (16.4)
Anaphylactic shock	9 (14.8)
Hypersensitivity	6 (9.84)
Nausea	6 (9.84)
Dizziness	5 (8.2)
Dysphagia	5 (8.2)
Flushing	5 (8.2)
Chest pain	4 (6.56)
Dyspnea	4 (6.56)
Lip swelling	4 (6.56)
Throat tightness	4 (6.56)
Among Serious[3]Reports	N = 39
Guillain Barré syndrome	12 (30.8)
Muscular weakness	12 (30.8)
Gait disturbance	11 (28.2)
Dyspnea	9 (23.1)
Anaphylactic shock	8 (20.5)
Cough	8 (20.5)
Grip strength decreased	8 (20.5)
Hypoaesthesia	8 (20.5)
Paraesthesia	8 (20.5)
Fatigue	7 (17.9)
Nausea	7 (17.9)
Pain in extremity	7 (17.9)

[1] Adverse events are listed as MedDRA preferred terms (PTs).
[2] A single report may contain more than one adverse event/PT (i.e., not mutually exclusive), therefore percentages may sum to greater than 100%.
[3] Reports are classified as serious based on the Code of Federal Regulations if one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization, permanent disability, or a congenital anomaly.

deteriorated with development of multi-organ failure and following multiple cardiac arrests, resuscitation attempts were unsuccessful. The cause of death was determined to be septic shock due to severe bilateral community acquired pneumonia.

3.2.2. Guillain Barré syndrome (GBS)

We identified 12 reports of GBS following adenovirus vaccine; two patients were female, and two of the remaining ten male patients were included in the military observational study. Prior to the onset of neurologic symptoms, eight of the 12 patients were documented with an upper respiratory infection and two patients were noted with a diagnosis of Bell's palsy (Table 4). The median age was 22 years (range 17–28). The median duration from vaccination until onset of initial symptoms was 24 days (range 9–42). All patients were hospitalized and received treatment with intravenous immunoglobulin (IVIG) and/or corticosteroids and recovered; however, four required ICU admission and were intubated. The following Brighton levels were assigned: Level 1 (n = 2), Level 2 (n = 6), and Level 3 (n = 4) (Table 4).

3.2.3. Hereditary Neuropathy with Liability to Pressure Palsy (HNPP)

We identified two serious reports of patients diagnosed with HNPP following adenovirus vaccine who required hospitalization. One 19-year-old female patient had an upper respiratory infection prior to the onset of her neurologic symptoms. The second patient was a 20-year-old male patient. We also identified a third report of HNPP in a 17-year-old male patient; this was classified as non-serious because the patient presented to the ED and subsequently was followed in the clinic. The three patients all presented within 4–8 days following exposure to multiple vaccinations with a history of progressive muscle weakness, numbness and paresthesia, received a presumptive diagnosis of GBS and were treated with IVIG and/or corticosteroid therapy (the latter was associated with temporary symptom relief in one patient) (Table 5). However, on clinical neurologic examination there was evidence of peripheral motor and sensory involvement, electromyogram/nerve conduction studies found slowing of multiple motor and sensory nerves consistent with a diagnosis of peripheral polyneuropathy, but no evidence of radiculopathy and myopathy on needle exam. In all these cases, genetic testing demonstrated deletion at chromosome 17p11.2–12, containing the peripheral myelin protein 22 (*PMP22*) gene, confirming the diagnosis of HNPP [25].

3.2.4. Anaphylaxis/hypersensitivity

We identified eight reports of anaphylaxis following adenovirus vaccine classified as serious and on review of medical records all were identified as participants in the military observational study. In two patients the anaphylaxis was considered as possibly related to vaccines; in one patient who required hospitalization, the episode followed exposure to the following vaccines: adenovirus, Tdap, inactivated influenza (IIV), inactivated poliovirus (IPV) and meningococcal conjugate (MCV4), and this patient had a past history of anaphylaxis following Tdap and hepatitis A vaccines (i.e., a missed contraindication for Tdap); in the second patient onset of symptoms occurred one day following concurrent receipt of the following vaccines: adenovirus, live attenuated influenza (LAIV), Tdap, and MCV4. In six patients anaphylaxis was considered unrelated to vaccine exposure based either on the onset of symptoms 1) without other exposures: one day prior to vaccination (n = 1), 3 weeks following vaccination (n = 1), or 2) with another possible exposure: insect (wasp, fire ants) venom exposure one day post vaccination (n = 2), exercise or environmental exposure one day post vaccination (n = 1), and exposure to trimethoprim sulfamethoxazole (TM-SMX) therapy for a urinary tract infection at the same time as vaccination (n = 1). In two reports, the patient with onset of anaphylaxis one day prior to vaccine administration and the patient in whom there was a potential drug reaction to TM-SMX therapy, co-administration of intramuscular penicillin G was documented. Limited information was available on these cases; only one report (case following exercise or environmental exposure) met a Brighton Collaboration case definition for anaphylaxis (Level 2).

Our review of all reports with the SOC immune system disorders identified 45 non-serious reports and several had information sufficient for meeting the criteria for anaphylaxis: 13 (29%) met a Brighton Collaboration case definition including: Level 1 (n = 4), Level 2 (n = 7), Level 3 (n = 2). All non-serious reports indicated exposure to multiple vaccines (median 5, range 4–7) and 32 (73%) documented co-administration of penicillin G. Specific therapy to treat anaphylaxis was reported administered in 32 (71%) reports including: epinephrine plus other drugs (16 reports which included all 10 military observational study non serious reports), antihistamine alone (n = 11), and antihistamine plus corticosteroid (n = 5). Two reports described anaphylaxis in patients with a prior history of penicillin allergy; the first was included in the observational study and developed anaphylaxis (Level 2) 1 day after receipt of adenovirus, Tdap, MCV4, IIV vaccines and penicillin G; however, this was not considered related to the vaccine exposures, and the second described a patient with a history of anaphylaxis following penicillin who developed anaphylaxis (Level 3) 5–10 minutes following receipt of adenovirus, hepatitis B, Tdap and MCV vaccines and intramuscular penicillin G and required admission to ICU. Each of these patients was treated with epinephrine, antihistamine and corticosteroid therapy.

3.2.5. Pregnancy

We identified one report of a 24-year-old female who had a negative hCG pregnancy test the day she received IIV, IPV, MCV4,

Table 4
Selected clinical findings of Guillain Barré syndrome patients reported in VAERS following Adenovirus Type 4 and Type 7 Vaccine, Live, Oral, October 2011 through July 2018.

Case and Year	Age (Yr) Sex	Recent History of Illness	Vaccines	Onset after Adenovirus vaccination (days)	Diminished DTR	CSF	EMG and NCS	Diagnosis	Treatment	Brighton level
1 2011	24M	URTI/sinusitis	Adeno Hep A Hep B MMR Varicella (5 days prior IPV IIV MCV4)	31	√	2 wbc normal protein	Consistent with AIDP/GBS	GBS	IVIG	2
2 2011 OBS STUDY	19-24M	URTI	Adeno (24 days prior MCV4 Tdap IIV Hep A)	2	√	Normal	Consistent with GBS/AIDP	GBS	IVIG	2
3 2011 OBS STUDY	~22M	URTI (1-2 weeks prior to onset of weakness)	Adeno Hep A (5 days prior IIV Tdap MCV4 IPV)	31	√	Normal	Consistent with AIDP/GBS	GBS	IVIG	2
4 2012	18M	URTI	Adeno Hep A/Hep B MCV4 Tdap	9	√	Not done	Consistent with AIDP/GBS	GBS	IVIG Prednisolone	2
5 2012	27M	URTI (1 week prior to onset of weakness)	Adeno LAIV Tdap Hep A/Hep B MCV4 Varicella (35 days later Hep A/Hep B IPV Varicella)	42	√	1 wbc normal protein	No record	GBS	IVIG	3
6 2012	20M	URTI/sinusitis (2 weeks prior to onset of weakness)	Adeno IIV IPV MCV4 Tdap (1 day prior Hep B MMR Varicella and 6 days later Hep A)	32	√	2 wbc elevated protein	Inflammatory neuropathy	GBS	IVIG	1
7 2013	19F	None	Adeno Hep A/Hep B LAIV MCV4 Tdap	9	√	2483 rbc elevated protein (traumatic LP)	No record (discussed with neurology team)	GBS	IVIG	3
8 2014	28F	None	Adeno Tdap MCV4 IIV	19	√	0 wbc normal protein	Mild sensory neuropathy	Atypical GBS	IVIG	2
9 2014	25M	URTI	Adeno MCV4 Tdap	25	√	100 wbc† normal protein	AMSAN	GBS AMSAN	IVIG	2

Table 4 (*continued*)

Case and Year	Age (Yr) Sex	Recent History of Illness	Vaccines	Onset after Adenovirus vaccination (days)	Diminished DTR	CSF	EMG and NCS	Diagnosis	Treatment	Brighton level
10 2015	17M	URTI	Adeno LAIV MMR Tdap MCV4 (4 days later Varicella)	31	√	Not done	No record	GBS	IVIG	3
11 2015	22M	Bell's palsy treated with prednisolone and valacyclovir	Adeno Hep A LAIV Varicella Tdap MCV4	15	Normal DTRs	0 wbc elevated protein	Mild axonal involvement	GBS	IVIG	1
12 2017	19M	Bell's palsy treated with prednisolone	Adeno Tdap Varicella IPV Hep A/Hep B MCV4 IIV MMR	27	√	Hemolyzed specimen	Not done	Miller Fisher syndrome	Steroid taper	3

Abbreviations used in this table: Yr = year, DTR = deep tendon reflexes, CSF = cerebrospinal fluid, EMG and NCS = electromyogram and nerve conduction study, M = male, F = female, URTI = upper respiratory tract infection, Adeno = adenovirus vaccine, Hep A = hepatitis A vaccine, Hep B = hepatitis B vaccine, MMR = measles mumps and rubella vaccine, IPV = inactivated poliovirus vaccine, IIV = inactivated influenza vaccine, MCV4 = meningococcal conjugate vaccine, √ = diminished DTRs, wbc = white blood cell, AIDP = acute inflammatory demyelinating polyneuropathy, GBS = Guillain Barré syndrome, IVIG = intravenous immunoglobulin, OBS = patient included in observational study, Tdap = tetanus diphtheria attenuated pertussis vaccine, Hep A/Hep B = combined hepatitis A and B vaccine, LAIV = live attenuated influenza vaccine, LP = lumbar puncture, AMSAN = acute motor sensory axonal neuropathy.

† Brighton criterion for cytoalbuminologic dissociation is CSF protein elevation above laboratory normal value and CSF total wbc count <50 cells/ul.

Table 5
Selected clinical findings of Hereditary Neuropathy with liability to Pressure Palsy (HNPP) patients reported in VAERS following Adenovirus Type4 and Type 7 Vaccine, Live, Oral, October 2011 through July 2018.

Case/ Year	Age (Yr) Sex	Recent History of Illness	Vaccines	Onset after Adenovirus vaccination (days)	Diminished DTR	CSF	EMG and NCS	Treatment	Genetic testing	Diagnosis
1 2016	20M	None	Adeno Hep A IIV IPV MCV4 Tdap Varicella	7	Normal	Not done	Acute demyelinating polyneuropathy on nerve conduction study	IVIG for presumed GBS	Positive for PMP22 gene deletion	HNPP
2 2016	17M	None	Hep B IIV Tdap MCV4 Tdap Adeno	8	√	Not done	Acute demyelinating polyneuropathy on nerve conduction study	6 day steroid course initially	Positive for PMP22 gene deletion	HNPP
3 2016	19F	URTI	Adeno Hep A IIV IPV MCV4 MMR Tdap Varicella	4	√	Not done	Acute demyelinating polyneuropathy on nerve conduction study	IVIG for presumed GBS	Positive for PMP22 gene deletion	HNPP

Abbreviations used in this table: Yr = year, DTR = deep tendon reflexes, CSF = cerebrospinal fluid, EMG and NCS = electromyogram and nerve conduction study, M = male, F = female, Adeno = adenovirus vaccine, Hep A = hepatitis A vaccine, IIV = inactivated influenza vaccine, IPV = inactivated poliovirus vaccine, MCV4 = meningococcal conjugate vaccine, Tdap = tetanus diphtheria attenuated pertussis vaccine, IVIG = intravenous immunoglobulin, GBS = Guillain Barré syndrome, PMP22 = peripheral myelin protein 22, HNPP = hereditary neuropathy with liability to pressure palsy, Hep B = hepatitis B vaccine, √ = diminished DTRs, URTI = upper respiratory tract infection, MMR = measles mumps and rubella vaccine.

and Tdap vaccines. One week later, she received adenovirus vaccine, hepatitis A/B vaccine, and intramuscular penicillin G. Nineteen days later she developed nausea, anorexia and light headedness and was found to have a positive hCG pregnancy test. Her last normal menstrual period began 29 days prior to the receipt of the adenovirus oral vaccine. On follow up the woman delivered a healthy infant.

3.3. Non adenovirus type 4 and type 7 vaccine, live, oral VAERS reports

VAERS received a total of 1055 reports from the proxy military recruit population which were reports following other vaccines during the period the adenovirus vaccine was unavailable. Among this group, the most commonly administered vaccines included: smallpox (41%), anthrax (39%), seasonal influenza (21%), and inactivated typhoid (16%). Among these non-adenovirus vaccine reports, 189 (18%) were classified as serious.

4. Discussion

Our review of adenovirus vaccine reports to VAERS is notable for the finding of a relatively higher percentage of reports classified as serious compared to reports for other vaccines in our proxy recruit military personnel population during the period when the adenovirus vaccine was unavailable (39% vs 18%). However, 17 (44%) serious adenovirus vaccine (including all eight anaphylaxis) reports were in the observational study. No serious anaphylaxis reports were identified among persons who were not included in the military observational study. In addition, 95% of the adenovirus vaccine reports documented co-administration of other vaccines and 50% reported co-administration of penicillin G (or other antibiotic if allergic to penicillin) according to standard DoD protocol in this military population. The investigators of the earlier military observational study also commented that concurrent vaccine exposures in the recruit population was an important limiting factor for attributing the statistical signaling outcomes including psoriasis, anaphylaxis and other hypersensitivity reactions as possibly related to the vaccine [18]. Also, our review of 53 hypersensitivity reports, which included eight serious anaphylaxis reports, identified 34 reports in which it was stated that intramuscular penicillin G was co-administered with the vaccines. The DoD recruit population routinely is administered intramuscular penicillin G, or if allergic another antibiotic, at the same time as required vaccinations by the standard protocol as prophylaxis for streptococcal infections [26]. The current DoD guidance states that before administration, recruits will be questioned for any history of penicillin hypersensitivity, and if there is a history compatible with immediate or delayed reactions to penicillin, they will receive an alternate non-penicillin antibiotic prophylactic regimen [26]. However, the policy statement acknowledges that historically, the rate of penicillin allergy in the general population has been between 5% and 10% [26]. Although true penicillin allergy is considered to be rare with the frequency of anaphylaxis estimated at 1–5 per 10,000 exposed individuals, penicillin G is the most common cause of drug allergy and its course is unpredictable (i.e., an individual who has a history of tolerating penicillin earlier may have an allergic presentation on subsequent administration of the drug and vice versa) [27].

Our review identified GBS and HNPP as two adverse neurologic outcomes. Among the 12 GBS cases, all but two patients were documented with an upper respiratory infection (eight patients) or Bell's palsy diagnosis (two patients) prior to the onset of neurologic symptoms. The significance of the Bell's palsy diagnosis in these two cases is unclear as few clinical details were available; it is possible that they represent the rare Miller Fisher syndrome (a GBS variant) which typically presents with facial diplegia with or without limb weakness, paresthesia, and decreased or absent deep tendon reflexes and albumin-cytological dissociation, or alternatively, the diagnosis of Bells' palsy and GBS in these patients may both be secondary to an overlooked upper respiratory infection (influenza or influenza-like illness) since this is a known risk factor for Bell's palsy. A preceding respiratory or gastrointestinal (e.g., *Campylobacter jejuni*) infection is a known cause of GBS and vaccine exposure has not been convincingly shown to cause GBS with the exception of the 1976 influenza A pandemic strain [28].

An interesting outcome reported to VAERS following adenovirus vaccine was HNPP. HNPP is a rare potentially underdiagnosed autosomal dominant condition characterized by repeated focal pressure neuropathies such as carpal tunnel syndrome and peroneal palsy with foot drop [25]. Common symptoms include numbness, paresthesia, muscle weakness and muscle atrophy. In all three patients reported to VAERS following adenovirus vaccine, the initial diagnosis made was GBS, and only following extensive work up, including electromyogram/nerve conduction studies and specific genetic testing that demonstrated deletion at chromosome 17p11.2–12, containing the *PMP22* gene, was the diagnosis made of HNPP [25].

We searched the VAERS database for reports of HNPP following other vaccines and identified a case report published in 2017 of a 19-year-old male who had been in the U.S. Army for 9 months whose symptom onset started two weeks after seasonal influenza vaccination and 1 day after vigorous exercise [29]. A provisional diagnosis of GBS was made in the patient and he was treated with IVIG with minimal improvement. The history of symptom onset after vigorous exercise, the presence of high foot arches and scapular winging raised suspicion of HNPP, and on genetic testing he was found to have *PMP22* gene deletion, confirming the diagnosis of HNPP [29].

In addition a 2004 published case report described a 21-year-old female recruit with onset of neurologic symptoms on her first day of military physical training who with continued strenuous activity over 3 weeks developed significant disabilities [30]. On admission to a local hospital, she was diagnosed with atypical peripheral neuropathy of either chronic inflammatory demyelinating or multifocal type. She was treated initially with IV methylprednisolone without improvement. Subsequent findings from an extensive clinical work up included pronounced muscle atrophy and electrophysiological evidence of focal acute axonal damage. Unusual features of this case included the fulminant onset, evidence of focal axonal dysfunction and a protracted clinical course with severe neurologic deficits persisting at one year after onset [30]. This case's possible exposure to multiple antecedent vaccinations is likely; however, the 2004 publication year predates the availability of the new adenovirus vaccine in the military vaccination program. In summary from the information available, it is unclear whether prior vaccination(s) received by these four HNPP cases was simply coincidental or may have had a role in triggering onset of the symptoms and future studies to address this question would be hampered by the rarity of this diagnosis. Alternatively, being in basic training and engaging in forced strenuous physical activity for the first time (for some recruits) might be an unmasking event for this condition. Also, although the condition is rare, healthcare providers should be aware that early in its presentation it may be a source of diagnostic confusion with GBS.

Limitations of our review include those common to any spontaneous safety reporting system including underreporting, incompleteness of records, lack of denominator of doses administered to calculate rates and the inability to establish causality. Because of widespread universal vaccination in the recruit military population, the comparison for the proportion of serious reports to VAERS following other vaccines was earlier and not contemporaneous

with our analytic period. We are also limited in this safety review by the nature of the military recruit population which receives the adenovirus vaccine co-administered with multiple other vaccines and routinely administered prophylactic intramuscular penicillin G or other antibiotics. Recruits may also be at increased risk of injury and illness due to their housing and training environment.

5. Conclusions

The percentage of serious reports in VAERS following the adenovirus vaccine was higher than with other vaccines administered in the military recruit population (39% vs. 18%); however, we identified no unexpected or concerning pattern of adenovirus vaccine AEs. No serious anaphylaxis reports were identified among persons who were not included in the military observational study. Ninety five percent of reports documented co-administration of other vaccines and 50% reported co-administration of prophylactic intramuscular penicillin G or other antibiotics in this military population. These other exposures may have contributed to the GBS and anaphylaxis outcomes observed with the adenovirus vaccine. Future adenovirus vaccine safety studies in a population without these co-administrations would be helpful in clarifying the vaccine's safety profile.

Disclaimer

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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