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Live Adenovirus Types 4 and 7 Not Detected in the Blood of Vaccine Recipients

Lori N. Perry, MD, MPH; Kellie L. McMullen, PhD; Robert Coon, BS; Patrick J. Blair, PhD; Gary T. Brice, PhD

Author affiliations: Naval Health Research Center, San Diego, California, USA (L. Perry, K. McMullen, P. Blair, G. Brice); Quintiles Inc., San Diego, California, USA (R. Coon)

Institution where work was done: Naval Health Research Center

Corresponding author: Lori Perry, 140 Sylvester Rd, Bldg 320, San Diego, CA 92106, USA; phone: (240) 498-4537; fax: (619) 553-7981; email: lori.n.perry.mil@mail.mil

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To the Editor: Military recruits are highly susceptible to adenovirus-related respiratory infections, likely due to the unique operating environments and training-related stress and fatigue (1). The associated morbidity results in lost training days and although rare, even death (2). Adenovirus infections decreased dramatically at recruit training centers between 1971 and 1996 following immunization with enteric vaccines against adenovirus types 4 and 7 (3). However, the disease re-emerged when production ceased and vaccination was discontinued. In 2004, a clinical trial was initiated to test live, oral adenovirus types 4 and 7 vaccines in military recruits, followed by a phase III trial that resulted in Food and Drug Administration approval of the vaccines in 2011 (4). Vaccination was reinstated at recruit training centers beginning around October 2011.

Military recruits are an important source of blood donations for military treatment facilities for use in retired military and dependent populations, many of whom are immunocompromised. Adenovirus has been identified as an emerging pathogen in immunocompromised patients (5), however there are no published data regarding adenovirus vaccine-generated viremia. Currently, there is no published data regarding adenovirus vaccine-generated viremia, although there have been a few studies looking at viremia following administration of other live-virus vaccines. Wilkins, et. al. isolated rubella virus 10 days post-vaccination, and posit that viremia occurs in almost every susceptible recipient but is low grade, transient, or both (6). Another study of a live recombinant vaccine against West Nile Virus found that vaccine was cleared from the blood by day 10, with the mean number of viremic days between 3.7 and 5.1 (7). Finally, a 1966 study elucidated free virus in the blood as early as the third day following vaccination with type 2 oral poliovirus vaccine. Fifty-five percent of subjects

receiving this vaccine were shown to be viremic, although this often was interspersed with intervening viremia-free periods (8).

Currently, the de facto time to blood donation after live oral adenovirus vaccination is 30 days, which is a relatively arbitrary time frame that hinders blood donation activities at many recruit training centers. We conducted a study at Marine Corps Recruit Depot San Diego to determine the incidence and duration of vaccine-induced viremia, as well as identify any circulating strains of adenovirus.

Two hundred and forty-nine male recruits were enrolled at the male-only training facility. Pre vaccination blood samples were obtained upon arrival. Available data indicate that viremia is typically detected 3–10 days postvaccination; hence, blood samples were collected on postvaccination days 3 and 8 (6–8). Additionally, blood samples were collected on postvaccination days 30 and 61 for surveillance purposes.

Nucleic acid was isolated from serum samples with the MagNA Pure LC Total Nucleic Acid Isolation Kit (Roche, Indianapolis, IN, USA) according to manufacturer's instructions. Samples were tested on the ABI 7500 real time instrument using a laboratory developed real-time assay targeting the adenovirus penton. All samples were also tested for the PPIA housekeeping gene to account for viability of the sample, and positive and negative controls were run with each batch tested. Validation studies show the sensitivity of this assay to be 100% in respiratory adenovirus positive cultures with a detectable range of 15.00-40.00 CT level.

Of the 249 recruits, 160 were able to complete the study. The remaining 89 missed at least 1 blood draw appointment because of reasons other than illness. At baseline, no recruit entered training with adenovirus detectable in his blood. We obtained 218 (87.6%) day 3 and 203 (81.5%) day 8 postvaccination blood samples. We also obtained 212 (85.1%) day 30 and 195

46 (78.3%) day 61 postvaccination blood samples. No adenovirus was detectable in any sample at
47 any time.

48 These results show that there was no adenovirus vaccine–generated viremia in this trial,
49 and indicate that a blood donation from a vaccinated military member poses no additional threat
50 to immunocompromised patients.

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Conflict of Interest Declaration

Competing interests: None declared

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References

1. McNeill KM, Hendrix RM, Linder JL, Benton FR, Monteith SC, Tuchscherer MA, et al. Large, persistent epidemic of adenovirus type 4-associated acute respiratory disease in U.S. Army trainees. *Emerg Infect Dis.* 1999;5(6):798–801.
2. Dudding BA, Wagner SC, Zeller JA, Gmelich JT, French GR, Top FH. Fatal pneumonia associated with adenovirus type 7 in three military trainees. *N Engl J Med.* 1973;286:1289–92.
3. Gaydos CA, Gaydos JC. Adenovirus vaccines in the military. *Mil Med.* 1995;160:300–3.
4. Lyons A, Longfield J, Kuschner R, Straight T, Binn L, Seriwatana J, et al. A double-blind, placebo-controlled study of the safety and immunogenicity of live, oral type 4 and type 7 adenovirus vaccines in adults. *Vaccine.* 2008;26(23):2890–8.
5. Leen AM, Rooney CM. Adenovirus as an emerging pathogen in immunocompromised patients. *Br J Haematol.* 2005;128(2):135–44.
6. Wilkins J, Salvatore MA, Leedon JM, Portnoy B. Viremia in a recipient of HPV-77 rubella virus vaccine. *Calif Med.* 1969;110(3):224–7.
7. Monath TP, Liu J, Kanesa-Thasan N, Myers GA, Nichols R, Deary A, et al. A live, attenuated recombinant West Nile virus vaccine. *Proc Natl Acad Sci U S A.* 2006;103(17):6694–9.
8. Melnick JL, Proctor RO, Ocampo AR, Diwan AR, Ben-Porath E. Free and bound virus in serum after administration of oral poliovirus vaccine. *Am J Epidemiol.* 1966;84(2):329–42.

89 Address for correspondence: Lori Perry, Operational Infectious Diseases, Naval Health Research
90 Center, 140 Sylvester Rd, Bldg 320, San Diego, CA 92106 USA; email:
91 lori.n.perry.mil@mail.mil