Urgent Attention Needed to Restore Lapsed Adenovirus Vaccine Availability: A Letter Report

Committee on a Strategy for Minimizing the Impact of Naturally Occurring Infectious Diseases of Military Importance:Vaccine Issues in the U.S. Military, Medical Follow-up Agency

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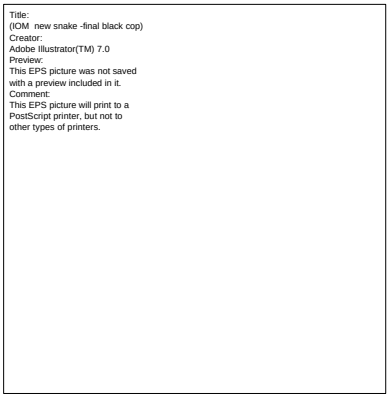
Willing is not enough; we must do."
Goethe



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COMMITTEE ON A STRATEGY FOR MINIMIZING THE IMPACT OF NATURALLY OCCURRING INFECTIOUS DISEASES OF MILITARY IMPORTANCE: VACCINE ISSUES IN THE U.S. MILITARY

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INDEPENDENT REPORT REVIEWERS

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

Robert B. Couch, M.D., Baylor College of Medicine
Bernard Gert, Ph.D., Dartmouth College
James W. LeDuc, Ph.D., Centers for Disease Control and Prevention
Adel A.F. Mahmoud, M.D., Ph.D., Merck & Co., Inc.
Bernhard T. Mittemeyer, M.D., Surgeon General, US Army, ret., Texas Tech University
William Schaffner, M.D., Vanderbilt University

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by D.A. Henderson M.D., M.P.H. of The Johns Hopkins University, appointed jointly by the Institute of Medicine and the NRC's Report Review Committee, who was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Urgent Attention Needed to Restore Lapsed Adenovirus Vaccine Availability

A Letter Report

Committee on a Strategy for Minimizing the Impact of
Naturally Occurring Infectious Diseases of Military Importance:
Vaccine Issues in the U.S. Military

Medical Follow-up Agency

INSTITUTE OF MEDICINE
Washington, D.C.

Urgent Attention Needed to Restore Lapsed Adenovirus Vaccine Availability

A Letter Report

November 6, 2000

Major General John Parker
Commanding General
U.S. Army Medical Research and Materiel Command
Fort Detrick, MD 21702-5012

Dear General Parker:

In April 2000, the Institute of Medicine of the National Academies convened an expert committee to advise the U.S. Army Medical Research and Materiel Command on the management of natural infectious disease threats to the military. The Committee on a Strategy for Minimizing the Impact of Naturally Occurring Infectious Diseases of Military Importance: Vaccine Issues in the U.S. Military will issue its complete report in January 2002. At its initial three meetings, the committee reviewed the failure of the Department of Defense (DoD) to maintain a supply of the adenovirus vaccine as an example of the problems DoD faces regarding the licensure, manufacture, and maintenance of special use vaccines. Production of this vaccine ceased in 1996 and stocks were depleted in 1999. What the committee heard was extremely disconcerting with respect to the threat that the lack of this vaccine now poses to the health of recruit populations. The committee submits this interim letter report today with a sense of extreme urgency in an effort to reinforce the view that there is a critical need for the DoD to expeditiously reestablish a process for the licensure, manufacture, purchase, and distribution of the adenovirus vaccine to military personnel undergoing recruit training activities.

The committee found:

- that the adenovirus vaccine is urgently needed to control the epidemic respiratory disease that has caused much morbidity among recruits in the past, and now once again threatens the health and even the lives of military trainees; since acute pulmonary infection due to adenovirus is a nearly unique occupational risk of the military trainee, it is imperative that DoD take rapid and effective action to once more eliminate this preventable disease;
- that the short-term, $14 million Defense Health Program commitment to acquiring an adenovirus vaccine is insufficient to stimulate the interest of capable commercial vaccine manufacturers; and
- that the existing acquisition and procurement systems within DoD are not structured to ensure continuing availability of limited use vaccines.

The committee recommends:

- that a much greater sense of urgency be placed on reacquiring an effective adenovirus vaccine;
- that a significantly larger and long-term commitment be made to restore and maintain the ongoing availability of adenovirus vaccine; and
- that the DoD not only evaluate the cause(s) underlying this serious procurement system failure, but also make a clear commitment to the changes necessary to prevent similar breakdowns in the future. In its final report to you, this committee will address system issues in depth in an attempt to help the Department of Defense define and then resolve the problem.

The basis for these findings and recommendations is presented in the text that follows.

INTRODUCTION

Capping 30 years of military medical research, the licensure of adenovirus type 4 and type 7 oral vaccines was a great success story. Epidemics of severe acute respiratory disease (ARD) had been a leading cause of hospitalization among recruits in Army, Navy, and Marine Corps training installations. In 1971, the first year of widespread use, adenovirus vaccines prevented an estimated 27,000 military hospitalizations. The risk of the severe ARD epidemics of the 1950s and 1960s was abolished. The impact of the vaccines, including a reduced need to recycle trainees who missed critical training due to hospitalization, as well as savings in the costs of medical care, made the vaccines extremely cost effective.[1]

As a result of a series of decisions that were made beginning in 1984 by Food and Drug Administration regulators, the manufacturer, and DoD officials, the sole manufacturer, Wyeth-Lederle Vaccines, ceased production of adenovirus vaccines in 1996.[2] Discussions between DoD and the manufacturer between 1984 and 1996 failed to lead to a mutually acceptable agreement that would have allowed continued vaccine availability. No alternative source of the vaccine has been found. The military was the only purchaser of adenovirus vaccine and limited its use to recruits in training operations; no civilian market exists at present for this vaccine.

IMPACT ON THE ARMED FORCES

Military surveillance data show minimal adenovirus-related morbidity during the period when the adenovirus vaccine was available and used at the training installations, followed by increased infection rates and hospitalization as vaccine administration became limited and finally ceased. Between October 1996 and May 1998, among symptomatic trainees at four sites, those who did not receive type 4 and 7 vaccine were 13 times more likely to have a positive adenovirus culture and 28 times more likely to be positive for type 4 or 7 adenovirus.[3] Ft. Jackson, Ft. Gordon, NTC Great Lakes, Cape May, Ft. Leonard Wood, Lackland AFB, and, most recently, Ft. Benning, have reported adenovirus epidemics, some with serious morbidity. Some epidemics have required adjustments such as the realignment of resources to convert barracks to infirmaries, the opening of new infirmary wards, the cancellation of elective surgeries, and staffing shifts. A few training camps have seen increases—20-fold at one base—in recruit recycling, when recruits miss enough of the training program that they need to begin again. The published surveillance data graphically show the temporal relationship between vaccine administration and respiratory disease rates in training camps.[4]

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[1]Russell PK. Adenovirus infection is not trivial. *U.S. Medicine*, November 1998.

[2]Barraza EM, Ludwig SL, Gaydos JC, Brundage JF. Reemergence of adenovirus type 4 acute respiratory disease in military trainees: Report of an outbreak during a lapse in vaccination. *Journal of Infectious Diseases* 179, 1999.

[3]Gray GC, Goswani PR, Malasig MD, Hawksworth AW, Trump DH, Ryan MA, Schnurr DP (for the Adenovirus Surveillance Group). Adult adenovirus infections: Loss of orphaned vaccines precipitates military respiratory disease epidemics. *Clinical Infectious Diseases* 31:663-670, September 2000.

[4]Gray et al., *ibid.*

In the 1950s and 1960s, before military scientists identified the causative viruses and developed this effective and safe oral vaccine,[5,6,7] approximately 50 percent of recruits fell ill with acute respiratory disease, with certain sites reporting 80 percent attack rates in some years. The vaccine program cut those rates, and the associated hospitalizations, in half. A 1998 cost-effectiveness analysis, using incidence data, a range of vaccination policy options, and medical and training cost data, estimated a savings of approximately $16 million per year were the DoD to reinstate the vaccine program.[8]

CURRENT DEVELOPMENT EFFORT

Attempts by the DoD to find an alternative solution, including initial negotiations with another vaccine manufacturer, have been unsuccessful to date. To restart an adenovirus-vaccine program, the new manufacturer must go through the full FDA new-product approval process. With a one-time $14 million investment from the Defense Health Program, the Medical Research and Materiel Command is preparing a Request for Proposals (RFP). Challenges include creating a contract strategy, with elements such as commitments to multi-year funding, to which manufacturers might respond. DoD anticipates releasing the RFP for comments in the fall of 2000, working toward the best-and-final offer stage in January 2001. Even without schedule slippage, a vaccine will not be available for use within the next three years.[9] The initial funding amount likely will cover only Phase I preparation and some administrative and technical support.[10]

DISCUSSION

- The DoD urgently needs adenovirus vaccine to (a) prevent increasingly large epidemics of febrile illness that put military personnel at risk of illness and even death,[11,12] and (b) avoid costs associated with medical care and disrupted or lost training days due to adenovirus illness.

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[5]Top FH Jr, Grossman RA, Bartelloni PJ, Segal HE, Dudding BA, Russell PK, Buescher EL. Immunization with live types 7 and 4 adenovirus vaccines. I. Safety, infectivity, antigenicity, and potency of adenovirus type 7 vaccine in humans. *Journal of Infectious Diseases* 124(2):148, August 1971.

[6]Rose HM, Lamson TH, Buescher EL. Adenoviral infection in military recruits: Emergence of type 7 and type 21 infections in recruits immunized with type 4 oral vaccine. *Arch Environ Health* 21:356, September 1970.

[7]Takafuji ET, Gaydos JC, Allen RG, Top FH Jr. Simultaneous administration of live, enteric-coated adenovirus types 4, 7, and 21 vaccines: Safety and immunogenicity. *Journal of Infectious Diseases* 140(1):48, July 1979.

[8]Howell MR, Nang RN, Gaydos CA, Gaydos JC. Prevention of adenoviral acute respiratory disease in Army recruits: Cost-effectiveness of a military vaccination policy. *American Journal of Preventive Medicine* 14(3), 1998.

[9]Howell W. Adenovirus history. Presentation to the Institute of Medicine Committee on a Strategy for Minimizing the Impact of Naturally Occurring Infectious Diseases of Military Importance: Vaccine Issues in the U.S. Military, September 2000.

[10]Howell W. Personal communication, October 2000.

[11]Levin S, Dietrich J, Guillory J. Fatal nonbacterial pneumonia associated with Adenovirus type 4: Occurrence in an adult. *Journal of the American Medical Association* 201:975, 1967.

[12] Dudding B, Wagner S, Zeller J. Fatal pneumonia associated with adenovirus type 7 in three military trainees. *New England Journal of Medicine* 286:1289, 1972.

- The military acquisition and procurement system has proven itself incapable of maintaining continuous availability of the adenovirus vaccine, and, in the opinion of the committee, its structure is inadequate to avoid similar failures for other limited use vaccine products.
- Although the commitment of $14 million of Defense Health Program funding is welcome, it is clearly not sufficient to reestablish licensure and ensure continued manufacture and purchase of an adenovirus vaccine. It seems unlikely that a commitment of this magnitude will be sufficient to bring competent, experienced manufacturers of vaccines into the negotiation process. The likelihood of restoring adenovirus vaccine to the military is significantly threatened by the lack of a longer range funding commitment.
- Reinstating the adenovirus vaccine program would be cost-effective. The monetary benefits of this vaccine's use unequivocably outweigh the high initial expenditures.

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Military service places young recruits in a uniquely high-risk setting for adenovirus infections during their training. Therefore, the Department of Defense has an obligation to protect recruits against this well-defined and largely preventable infection. To date, military training operations have not been perceived as significantly affected by adenovirus vaccine unavailability, as indicated by the relative lack of attention given the situation by upper-level commanders. However, the ongoing health surveillance, epidemiology, and military preventive medicine networks have gathered incontrovertible evidence of an impending public health emergency.

Sincerely,

Stanley M. Lemon, M.D. (*Chair*), for the Institute of Medicine
Committee on a Strategy for Minimizing the Impact of Naturally Occurring
Infectious Diseases of Military Importance: Vaccine Issues in the U.S. Military