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TITLE: 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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CONTRACTING ORGANIZATION: National Academy of Sciences
Washington, DC 20078-5576

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Fort Detrick, Maryland 21702-5012

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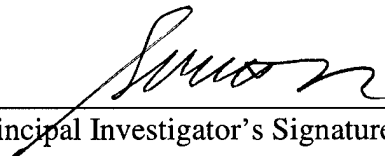
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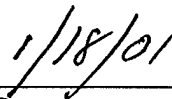
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Principal Investigator's Signature


Date

INTRODUCTION

In April 1999, at the request of COL Charles Hoke, Jr., Director, Military Infectious Diseases Research Program, and MG John Parker, Commanding General, U.S. Army Medical Research and Materiel Command, the Institute of Medicine of the National Academies appointed an expert committee with staff support from the Medical Follow-up Agency. The committee's name reflects USAMRMC's concerns: Committee on a Strategy for Minimizing the Impact of Naturally Occurring Infectious Diseases of Military Importance: Vaccine Issues in the U.S. Military.

Over the course of the project, the committee will meet approximately five times to gather information—from invited speakers and discussants representing DOD and other Federal agencies, and interested individuals active in academic research, clinical care, and the pharmaceutical and vaccine industry, as well as from peer-reviewed literature and reports. The charge to the committee derives from the work statement and accompanying material in the contract between DOD and IOM. It states that

[T]he committee will analyze available information, hold workshops and make specific recommendations on both technical and policy aspects regarding the Department of Defense (DoD) vaccine strategy to combat infectious diseases. The issues include: (1) reviewing the problem of the naturally occurring infectious diseases threat to military operations; (2) defining and prioritizing the diseases of relevance to the U.S. military; (3) determining the status of vaccines available to protect military personnel; (4) examining the Military Infectious Diseases Research Program (MIDRP), with particular emphasis on current disease priorities, vaccine product development, and the role of the MIDRP not only within the framework of the overall Military Acquisition model, but also among other Federal government infectious disease programs; (5) reviewing the roles, if any, that the MIDRP should play in the licensure, manufacture, and distribution of vaccines against diseases of military importance, in the context of current interrelationships within DoD and among other federal agencies, industry, and university research activities; and (6) developing recommendations for a comprehensive strategy and doctrine that MIDRP and DoD could adopt to best use their resources to contribute toward the goal of effective development, licensure, production, stockpiling, distribution, and use of vaccines against naturally occurring diseases of military importance. Other issues regarding vaccine strategies against infectious diseases are likely to be brought to the attention of the committee by the DoD.

The project's end-product will be a report by the committee that has been reviewed and approved by the IOM executive office and a panel of peer reviewers, under the guidelines and final authority of the National Research Council Report Review Committee.

This annual report covers the period December 7, 1999 to December 7, 2000.

FIRST YEAR ACTIVITIES

During the first year of this project, the Medical Follow-up Agency of the Institute of Medicine has assigned staff to this committee project; met with the sponsor's program staff (COL Charles Hoke, Jr., COL Rodney A. Michael, COL Lawrence Lightner, and LTC Colleen Martinez) to discuss the scope of the IOM committee project, sponsor expectations, and background material; consulted with people knowledgeable about vaccine development and use, infectious disease, military health needs, and others to gather names of prospective committee members; and invited 14 individuals who have agreed to serve on the committee. The committee and staff roster is attached (Appendix A).

The committee met four times (April 3-4, June 19-20, September 21-22, and November 13-14, 2000). At each of those meetings, the DOD sponsor representatives were guest participants along with other attendees. The agendas for those meetings are attached (Appendix B) as is the current, cumulative guest invitation list (Appendix C). In accordance with National Research Council guidelines relating to the Federal Advisory Committee Act, all meetings have been announced via the National Academies Current Project System on the World Wide Web.

Although the contract calls for only a final committee report, after hearing disturbing information at its first few meetings, the committee chose to issue a letter report to MG Parker regarding its concern about the unavailability of an adenovirus vaccine for troops in training camps. This letter, attached (Appendix D), was delivered to MG Parker on November 7, 2000 and made available to the public on November 13, 2000 when it was discussed, in open session, at the fourth meeting of the committee. The report is available via the National Academies website as a PDF file at http://books.nap.edu/html/adenovirus/adenovirus_letter.pdf.

PLANNED ACTIVITIES

The committee is scheduled to meet again on February 27-28, 2001 to work on material for the final report. The writing of the report will be an iterative procedure involving staff and committee members and will likely require another one or two meetings. When a draft is approved by the committee, staff will shepherd it through the report review process, submitting it to a panel of experts and responding as necessary until approval is confirmed by the National Research Council Report Review Committee. At that time, the Institute of Medicine will transmit the report to the sponsor (MG Parker and COL Hoke) and, after an appropriate period (usually one to two weeks), will release the report to the public.

APPENDICES

- A. Committee and staff roster
- B. Committee meeting agendas
 - 1) April 2000
 - 2) June 2000
 - 3) September 2000
 - 4) November 2000
- C. Current, cumulative guest invitation list
- D. Letter report titled "Urgent Attention Needed to Restore Lapsed Adenovirus Vaccine Availability," by the 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, the National Academies, dated November 6, 2000.

Annual Report for Contract DAMD17-00-C-0003
Submitted January 12, 2001 by
Susan Thaul, Ph.D., Study Director

APPENDIX A

THE NATIONAL ACADEMIES

Advisers to the Nation on Science, Engineering, and Medicine

National Academy of Sciences
National Academy of Engineering
Institute of Medicine
National Research Council

Medical Follow-up Agency
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

Committee

Stanley M. Lemon, M.D., *Chairman*
Dean of Medicine and Professor
University of Texas Medical Branch, Galveston, Texas

Charles C. J. Carpenter, M.D.
Professor of Medicine, Brown University, The Miriam Hospital, Providence, Rhode Island

Ciro A. de Quadros, M.D., M.P.H.
Director, Division of Vaccines and Immunization
Pan American Health Organization, Washington, D.C.

R. Gordon Douglas, Jr., M.D.
Princeton, New Jersey

Lawrence O. Gostin, J.D., LL.D. (Hon.)
Co-Director, Georgetown/Johns Hopkins Joint Program in Public Health and Law
and Professor of Law, Georgetown University, Washington, D.C.

M. Carolyn Hardegree, M.D.
Potomac, Maryland

Samuel L. Katz, M.D.
Wilburt C. Davison Professor and Chairman Emeritus
Duke University Medical Center, Durham, North Carolina

F. Marc LaForce, M.D.
BASICS2, Arlington, Virginia

Stanley A. Plotkin, M.D.
Doylestown, Pennsylvania

Gregory A. Poland, M.D.
Chief, Mayo Vaccine Research Group, Mayo Clinic and Foundation, Rochester, Minnesota

Committee, continued

N. Regina Rabinovich, M.D., M.P.H.
Director, Malaria Vaccine Initiative
Program for Appropriate Technology in Health, Rockville, Maryland

Philip K. Russell, M.D.
Potomac, Maryland

Ronald J. Saldarini, Ph.D.
Mahwah, New Jersey

Mary E. Wilson, M.D.
Chief of Infectious Diseases, Mount Auburn Hospital, Cambridge, Massachusetts
Associate Professor of Medicine, Harvard Medical School

Staff

Susan Thaul, Ph.D.
Study Director

Salem Fisseha
Research Assistant

Karen Kazmerzak
Research Assistant

Richard N. Miller, M.D., M.P.H.
Director, Medical Follow-up Agency

Heather O'Maonaigh, M.A.
Program Officer

Pamela Ramey-McCray
Administrative Assistant

1/12/2001

APPENDIX B



The Medical Follow-up Agency



Agenda

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

3 and 4 April 2000
1055 Thomas Jefferson Street, NW • Washington, DC
Room FO 2004



3 April 2000

Closed Session

- 8:00 Continental Breakfast
- 8:30 Introductory Remarks and Review of Charge
Richard Miller, Director, Medical Follow-up Agency
Stanley Lemon, Committee Chair
Susan Thaul, Study Director
- 8:45 Bias Discussion and Introductions:
Clyde Behney, Deputy Executive Officer, Institute of Medicine
- 9:45 Break

Open Session

- 10:00 Sponsor Presentation
- MG John S. Parker**, MD, Commanding General
U.S. Army Medical Research and Materiel Command (MRMC)
Charge to the IOM and Welcoming Remarks
- COL Charles H. Hoke, Jr.**, MD, Research Area Director
Military Infectious Diseases Research Program (MIDRP)
Overview of the Military Infectious Diseases Research Program

11:00 Break

11:15 Sponsor Presentation, continued

COL Rodney A. Michael, MD

Military Infectious Diseases Research Program
Overview of the DoD Research and Development (Acquisition) Model

COL John F. Glenn, PhD, Deputy for Research and Development

U.S. Army Medical Research and Materiel Command
Biologic Warfare Defense Research and Endemic Infectious Diseases Research:
Whence and why the dichotomy

12:15 Lunch

1:15 Discussion with Sponsor

Current challenges

Overview of the challenges to adequate vaccine strategy presented by industry
and DoD policies and constraints

Overview of the regulatory parameters that currently affect military vaccine
strategy

Discussion of what the U.S. Army seeks to gain from this committee report

Discussion of charge

2:15 Break

Closed Session

2:30 Introduction to the Committee and Report Review Process:

Claudia Carl, IOM Executive Office Representative

3:30 Committee Discussion

Questions about the committee process?

Review of the committee charge: how does the committee interpret the charge?

What questions does the committee have for the sponsor?

Other preliminary questions and concerns?

4:30 Concluding Remarks and Adjournment

5:30 Dinner for Committee and Staff (*La Chaumiere*, 2813 M Street, N.W.)

4 April 2000

Closed Session

8:30 Continental Breakfast

9:00 Review and Discussion of the Committee Charge: **Richard Miller**

9:30 Draft Outline of the Report: **Susan Thaul**

10:30 Break

10:45 Study Timeline, **Susan Thaul**

11:15 Writing Assignments

12:00 Working Lunch for Committee and Staff

1:00 Resource Requirements

Additional expertise needed (e.g., new technologies, economics, consumer)?

Writing consultant?

Liaison members?

Further presentations?

Data, documents, and readings?

2:30 Break

2:45 Scheduling Meeting and Writing Deadlines

3:30 Concluding Remarks and Adjournment



The Medical Follow-up Agency

Agenda

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

Second Meeting: 19 and 20 June 2000

1055 Thomas Jefferson Street, NW • Washington, DC • Room FO 2004

19 June 2000—Open Session

10:00 Welcome and Introduction, **Stan Lemon, MD, Chair**

10:05 EXAMPLES OF THE IMPACT OF VACCINE PREVENTABLE INFECTIOUS DISEASE

Impact of Recent Adenovirus Outbreaks in Military Training Centers

CAPT Gregory Gray, MD, MPH

*Director, DoD Center for Deployment Health Research
Naval Health Research Center, San Diego*

Lt Col James Neville, USAF, MC, FS

*Chief, Force Health Protection and Surveillance Branch
USAF Institute for Environment, Safety & Occupational Health Risk Analysis
Brooks AFB*

Leonard N. Binn, PhD

*Supervisory Research Microbiologist, Department of Virus Diseases
Walter Reed Army Institute of Research*

The Meningococcal Meningitis Situation, Military and Civilian

Civilian

Juliette Morgan, MD

*Medical Epidemiologist, Meningitis and Special Pathogens Branch
Centers for Disease Control and Prevention*

Military

John Brundage, MD

*Senior Research Epidemiologist, Henry M. Jackson Foundation
Army Medical Surveillance Activity, WRAIR*

11:30 JVAP—PROCUREMENT PROCESS FOR VACCINES FOR BIOWARFARE DEFENSE

Richard B. Paul, MA

Acting Program Manager, Joint Vaccine Acquisition Program

12:00 VACCINE DEVELOPMENT SUCCESS—POLICY FAILURE

Adenovirus Vaccine: Successful Development

Franklin H. Top, Jr., MD

Medimmune

Adenovirus Vaccine: A Policy Failure

Joel Gaydos, MD, MPH

*DoD Global Emerging Infections Surveillance & Response System,
Division of Preventive Medicine, Walter Reed Institute of Research*

12:45 Lunch (and continued discussion)

1:30 VACCINE RESEARCH & DEVELOPMENT: PRIORITY SETTING

DoD Requirements Generation and Acquisition

James H. Nelson, PhD

Director, U.S. Army Medical Materiel Development Activity

Military Medical Surveillance of Infectious Disease

LTC Mark V. Rubertone, MD

Chief, Army Medical Surveillance Activity

U.S. Army Center for Health Promotion and Preventive Medicine

Medical Intelligence

Deborah G. Keimig, PhD

Chief, Epidemiology and Environmental Health Division

Armed Forces Medical Intelligence Center, Fort Detrick

Priority Setting in Practice

COL Rodney A. Michael, MC

Deputy Director, Military Infectious Disease Research Program


Discussion

19 June 2000—Closed Session

4:30 Committee Discussion

5:30 Adjourn Meeting Day 1

6:00 Dinner for Committee and Staff (*Tahoga*, 2815 M Street, N.W.)


20 June 2000—Open Session

- 7:30 Continental Breakfast
- 8:00 Review of Meeting Day 1 and Introduction of Day 2 Program, **Stan Lemon, MD, Chair**
- 8:20 STATUS OF LIMITED USE VACCINES IN THE MILITARY
- U.S. Army Research Institute of Infectious Diseases
LTC Phillip R. Pittman, MD, MPH
Senior Medical Scientist
- 8:50 HOW OTHERS (TRY TO) MAKE LIMITED USE VACCINE DEVELOPMENT WORK
- Food and Drug Administration
Karen Goldenthal, MD
Director, Division of Vaccines & Related Products Applications
- National Institute of Allergy and Infectious Disease, National Institutes of Health
Carole A. Heilman, PhD
Director, Division of Microbiology and Infectious Diseases
- Centers for Disease Control and Prevention
James W. LeDuc, PhD
Acting Director, Division of Viral and Rickettsial Diseases
National Center for Infectious Diseases, CDC
- Industry Involvement in Federal Vaccine Development and Procurement Efforts
Thomas P. Monath, MD
Vice President, Research & Medical Affairs, OraVax Inc.
- Discussion: Constraints Faced and Handled
How Might DoD Use These Approaches
- 11:45 Lunch—with concurrent discussion based on morning's presentations

20 June 2000—Closed Session

- 1:00 Discussion of workshop presentations
- 1:30 Committee business
- Time line, meeting dates
 - Scope and report focus
 - Additional information needed
 - Writing assignments
- 2:00 Adjournment



The Medical Follow-up Agency

DRAFT (as of 9/15/00) Agenda

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

Third Meeting: 21 and 22 September 2000

1055 Thomas Jefferson Street, NW • Washington, DC • Room FO 2004

Thursday, September 21, 2000

Closed session

- 9 AM Continental breakfast *[staff meets with chair]*
- 10 AM Begin meeting
Review agenda
- 10:10 AM Introduce topics and set aside for discussion on Friday
Adenovirus vaccine letter report
DoD Acquisition of Vaccine Production Advisory Panel
Committee report draft pieces

Open session

- 11 AM Welcome
Stan Lemon, MD, Chair
- 11:05 AM ADENOVIRUS VACCINE
MAJ Michael Dyer, MPH
Office of the TRADOC Surgeon
William Howell
Deputy for Acquisition and Advanced Development
U.S. Army Medical Research and Materiel Command
- Noon Lunch
- 12:45 PM VACCINE PRODUCTION
Gary Nabel, MD, PhD
Director, NIH Vaccine Research Center
Dr. Jack Melling
RE: the old Salk Institute and British GOCO

- 2 PM PRIORITIES
- LTC Brian G. Scott**
Clinical Consultant, Force Protection
AMEDD Center and School
Directorate of Combat and Doctrine Development
- COL John Frazier Glenn**
Deputy for R&D at MRMC
- Discussion: Presenters and
COL Charles Hoke, Jr., MD
COL Rodney Michael, MD
- 4 PM Discussion
- 5 PM Adjourn for the day
- 6 PM Committee and staff dinner at local restaurant

◆

Friday, September 22, 2000

Closed session

- 8 AM Continental breakfast
- 8:30 AM DoD Acquisition of Vaccine Production Advisory Panel
Richard Miller, MD, MPH
- 9 AM Report on the September 2000 Armed Forces Epidemiology Board meeting
Marc LaForce, MD
- 9:30 AM Adenovirus vaccine letter report or other action
Decide whether to produce a letter report to MG Parker at MRMC
[If yes:] Review and revise draft
- 11 AM Planning
Reassess pre-meeting written summaries and material.
Revise outline for report chapters.
Assign sections and due dates.
Create timetable.
Discuss future meeting dates.
- Noon Lunch
- 1 PM Discussion, work continues
- 3 PM Adjourn



The Medical Follow-up Agency

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

Fourth Meeting: 13 and 14 November 2000

1055 Thomas Jefferson Street, NW • Washington, DC • Room FO 2004

Monday, November 13, 2000

OPEN SESSION

- 9:30 AM Continental breakfast in conference room
- 10 AM Review agenda, introduce speakers
- 10:10 AM Incentivizing limited use vaccine production: getting and keeping vaccines
Kevin F. Reilly
President, Wyeth Vaccines and Nutrition
Wyeth-Ayerst Pharmaceuticals
- 11:30 AM Public release of this committee's interim report:
*Urgent Attention Needed to Restore Lapsed Adenovirus Vaccine Availability:
A Letter Report*
Stanley Lemon
IOM Committee Chair
- Adenovirus update
CDR Jeff Yund, MC (FS)
Division of Preventive Medicine and Occupational Health
U.S. Navy Bureau of Medicine and Surgery
- 12:30 PM Working lunch in conference room for committee, staff, and guests
- 1:30 PM Priority setting revisited (panel discussion)
COL John Frazier Glenn
Deputy for Research and Development
U.S. Army Medical Research and Materiel Command
- LTC Brian G. Scott**
Clinical Consultant, Force Protection
Directorate of Combat and Doctrine Development
AMEDD Center & School
- COL Charles Hoke, Jr.**
Director, Military Infectious Diseases Research Program
U.S. Army Medical Research and Materiel Command
- 3 PM Open session ends

Monday, November 13, 2000, continued

CLOSED SESSION

3:15 PM Discussion
5 PM Adjourn for the day
6 PM Committee and staff dinner at Asia Nora, 2213 M Street NW



Tuesday, November 14, 2000

CLOSED SESSION

8 AM Continental breakfast
8:30 AM Scheduling: Future meetings and writing deadlines
8:40 AM Committee discussion: Yesterday's presentations and discussions
10 AM Committee discussion: Report outline and committee-member drafts
12 PM Working lunch in conference room
1 PM Writing group working sessions (at chair's discretion)
3 PM Adjourn

APPENDIX C

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

Master Invitation List, alphabetized, as of November 9, 2000

General John Abrams
Commanding General
US Army Training and Doctrine Command
Fort Monroe, Virginia

William H. Bancroft, MD
Medical Scientist
Science Applications International Corporation
Frederick, Maryland

COL John 'Rich' Barrett, MC
Division of Operational Medicine
U.S. Army Medical Research Institute of Infectious Diseases
Ft. Detrick, Maryland

Leonard N. Binn, PhD
Supervisory Research Microbiologist
Department of Virus Diseases
Walter Reed Army Institute of Research
Silver Spring, Maryland

John Boslego, MD
Merck

COL Dana Bradshaw
representing Bgen Lloyd Dodd
DoD Reliance Panel Chair
and Member ASBREM Steering Group

Brenda L. Brandt
Walter Reed Army Institute of Research
Washington, D.C.

John Brundage, MD
Jackson Foundation
Walter Reed Army Institute of Research

Donald Burke, MD
Department of International Health
Center for Immunization Research
Johns Hopkins School of Public Health

COL David Danley
Selected Program Manager
Joint Vaccine Acquisition Program
Ft. Detrick, Maryland

COL Bob F. DeFraitess
U.S. Army Center for Health Promotion and Preventive Medicine
Washington, D.C.

COL Benedict M. Diniega, MD, MPH
Executive Secretary
Department of Defense (Health Affairs)
Armed Forces Epidemiological Board
Falls Church, Virginia

MAJ Michael Dyer
Office of the TRADOC Surgeon
Fort Monroe, Virginia

RADM Noel K. Dysart
Bureau of Medicine and Surgery
Member ASBREM Steering Group

Dr. Ken Eckels
Chief, Dept Biologics Research
Walter Reed Army Institute of Research

William M. Egan, PhD
Director, Office of Vaccines Research and Review
Center for Biologics Evaluation and Research
Food and Drug Administration

COL Edward M. Eitzen, Jr., MC
Chief, Division of Operational Medicine
U.S. Army Medical Research Institute of Infectious Diseases
Ft. Detrick, Maryland

LTC Brian H. Feighner
Injuries & Occupational Illnesses Office
Epidemiology and Disease Surveillance
U.S. Army Center for Health Promotion and Preventive Medicine
Aberdeen Proving Ground, Maryland

Thomas C. Fileccia
Acting Director
Pharmaceuticals Group
Defense Supply Center Philadelphia

Dr. Robert Foster
Director Biosystems
OUSD(AT) DDRE representing DUSD(S&T)

Joel C. Gaydos, MD, MPH
DoD Global Emerging Infections Surveillance & Response System
Division of Preventive Medicine
Walter Reed Army Institute of Research

COL Jeffrey Gere
Commander, U.S. Army Medical Materiel Development Activity
Ft. Detrick, Maryland

COL John Frazier Glenn
Deputy for R&D
US Army Medical Research and Materiel Command

Karen L. Goldenthal, MD
Division of Vaccines & Related Products Applications
Center for Biologics Evaluation and Research
Food and Drug Administration

LTC John D. Grabenstein, RPh, PhD
Deputy Director for Clinical Operations
Anthrax Vaccine Immunization Program Agency
U.S. Army Medical Command
Falls Church, Virginia

CAPT Gregory C. Gray, MD, MPH
Captain Medical Corps, United States Navy
Director, DoD Center for Deployment Health Research
Naval Health Research Center
San Diego, California

R. Kevin Hanson
Director, General Preventive Medicine Residency
Uniformed Services University of the Health Sciences

Carole A. Heilman, PhD
Director, Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases

Craig Hendrix, MD
Associate Professor of Medicine, Pharmacology, and Epidemiology
Johns Hopkins

Dr. Edward L. Hoedebecke
U.S. Army Center for Health Promotion and Preventive Medicine

Paul Hoeper
Assistant Secretary of the Army for Acquisition, Logistics, and Technology
ASA(ALT)

Stephen L. Hoffman, MD DTMH CAPT MC USNR
Director, Malaria Program
Naval Medical Research Institute

COL Charles H. Hoke Jr., MC
Director, Military Infectious Diseases Research Program
Ft. Detrick, Maryland

William Howell
Deputy for Acquisition and Advanced Development
U.S. Army Medical Research and Materiel Command

Deborah G. Keimig, PhD
Chief, Epidemiology and Environmental Health Division
Armed Forces Medical Intelligence Center
Defense Intelligence Agency
Fort Detrick, Frederick, Maryland

COL Patrick W. Kelley, MC
Director, Division of Preventive Medicine and
DoD Global Emerging Infections Surveillance and Response System
Walter Reed Army Institute of Research
Division of Preventive Medicine
Silver Spring, Maryland

Dr. Shellie A. Kolavic
U.S. Army Center for Health Promotion and Preventive Medicine

LTC George W. Korch
U.S. Army Medical Research Institute of Infectious Diseases

James W. LeDuc, PhD
Acting Director, Division of Viral and Rickettsial Diseases
National Center for Infectious Diseases
Centers for Disease Control and Prevention
Atlanta, Georgia

COL Lawrence K Lightner, PhD
Associate Director, Military Infectious Diseases Research Program
Ft. Detrick, Maryland

Dr. Carol D. Linden
U.S. Army Medical Research Institute of Infectious Diseases

LTC Coleen K. Martinez, PhD
Assistant Director, Military Infectious Diseases Research Program
Ft. Detrick, Maryland

Mr. Steve McManus
Director, Pharmaceuticals Group
Defense Supply Center, Philadelphia

Mike McNeil, MD
Anthrax Vaccine Research Program
Epidemiology and Surveillance Division
National Immunization Program
Centers for Disease Control and Prevention
Atlanta, Georgia

Dr. Jack Melling
RE: the old Salk Institute and British GOCO

COL Rodney A. Michael, MC
Deputy Director, Military Infectious Disease Research Program
Ft. Detrick, Maryland

Thomas P. Monath, MD
Vice President, Research & Medical Affairs
OraVax Inc. (subsidiary of Peptide Therapeutics Plc)
Cambridge, Massachusetts

Juliette Morgan, MD
Medical Epidemiologist
Meningitis and Special Pathogens Branch
Centers for Disease Control and Prevention
Atlanta, Georgia

Gary Nabel, MD, PhD
Director, NIH Vaccine Research Center

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James Neville, Lt Col, USAF, MC, FS
Chief, Force Health Protection and Surveillance Branch
USAF Institute for Environment, Safety & Occupational Health Risk Analysis
Brooks AFB Texas

COL Gerald W. Parker
U.S. Army Medical Research Institute of Infectious Diseases

MG John Parker, MD
Commanding General
U.S. Army Medical Research and Materiel Command

Richard B. Paul, MA
Acting Program Manager, Joint Vaccine Acquisition Program
Ft. Detrick, Maryland

LTC Phillip Pittman, MC
Senior Medical Scientist
U.S. Army Medical Research Institute of Infectious Diseases

LtCol James R. Riddle, USAF
Program Director, Military Public Health
OASD/HA (Clinical and Program Policy)

LTC Mark V. Rubertone, MC
Chief, Army Medical Surveillance Activity
U.S. Army Center for Health Promotion and Preventive Medicine
Washington, D.C.

COL Jose L. Sanchez, MC
Program Manager, Epidemiology Services Program
US Army Center for Health Promotion & Preventive Medicine
Aberdeen Proving Ground, Maryland

LTC Brian Scott
Clinical Consultant, Force Protection
Directorate of Combat and Doctrine Development
AMEDD Center and School

COL Thomas Smith
TRADOC Surgeon
Fort Monroe, Virginia

Nancy Tomich
US Medicine

Franklin H. Top, Jr., MD
Medimmune
Gaithersburg, Maryland

Dr. Andy Towle
VaccGen, International, Inc.

CAPT David Trump
Clinical Services, Health Affairs
Department of Defense

LTC David W. Vaughn
Chief, Virus Diseases Department
Walter Reed Army Institute of Research

Dr. Wendell D. Zollinger
Walter Reed Army Institute of Research
Washington, D.C.

Kathryn C. Zoon, PhD
Director, Center for Biologics Evaluation and Research
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APPENDIX D

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

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

²Barraza 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.

³Gray 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.

⁴Gray 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.

⁵Top 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.

⁶Rose 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.

⁷Takafuji 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.

⁸Howell 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.

⁹Howell 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.

¹⁰Howell W. Personal communication, October 2000.

¹¹Levin 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.

¹²Dudding 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 unequivocally outweigh the high initial expenditures.



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

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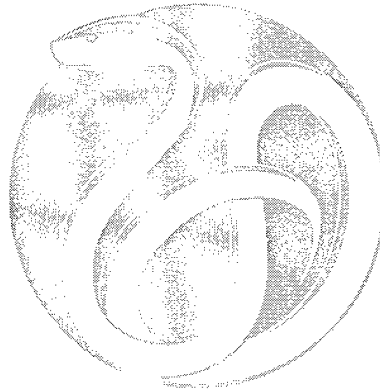
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Willing is not enough; we must do."
—Goethe*



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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:

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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.