DEPARTMENT OF DEFENSE
ARMED FORCES EPIDEMIOLOGICAL BOARD
5109 LEESBURG PIKE
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AFEB (15-1a) 00-9

03 August 2000

MEMORANDUM FOR THE ASSISTANT SECRETARY OF DEFENSE (HEALTH AFFAIRS)
THE SURGEON GENERAL, DEPARTMENT OF THE ARMY
THE SURGEON GENERAL, DEPARTMENT OF THE NAVY
THE SURGEON GENERAL, DEPARTMENT OF THE AIR FORCE

SUBJECT: Antibiotics Against Biowarfare Agents

1. On March 13, 2000 the Deputy Assistant Secretary of Defense for Health Operations Policy requested that the Armed Forces Epidemiological Board, in consultation with the Centers for Disease Control and Prevention (CDC), provide recommendations on the most appropriate FDA approved antibiotics to be used for treatment of the primary bacterial and rickettsial agents on the biowarfare threat list. Specifically, recommendations were requested for treatment of the organisms which cause anthrax, plague, tularemia, brucellosis, glanders, and Q fever.

2. The selection of antibiotics to prevent and treat illness from biowarfare agents has received considerable recent attention. In December 1999, a Medical Biological Defense Material (MBDM) policy meeting was held at Fort Detrick, Maryland to develop a list of preferred antibiotics for post-exposure prophylaxis. A triservice field manual "Treatment of Biological Warfare Agent Casualties," which includes antibiotic recommendations, has recently been finalized. CDC is developing a civilian pharmaceutical stockpile for prevention and treatment of illness due to large-scale bioterrorism and has also addressed the issue. Beginning in 1999, the Journal of the American Medical Association (JAMA) has begun publishing a series of articles on biological warfare agents, including treatment and prophylaxis, based on the recommendations of a Working Group on Civilian Biodefense constituted by The Johns Hopkins School of Public Health. During the May 2000 AFEB meeting, the Board heard a presentation on this topic by LtCol George Christopher from the US Army Medical Institute of Infectious Diseases, who led the effort to develop the triservice field manual, and discussed the issues with the Board and the Disease Control Subcommittee.

3. In developing the list of recommended agents, the Board reviewed the above materials and considered the following issues:

- Efficacy of the drugs against the threat agents based on peer-reviewed publications and other data sources
- Potential for antimicrobial resistance (natural and bioengineered)
- Side effects profiles of the alternative antimicrobial agents
- Ease of administration (especially dosing frequency)
- Broadness of spectrum (how many agents would be covered)
- Interactions with other drugs or products which may be used simultaneously
- Cost (including potential changes in cost as patents lapse)
- Shelf life

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4. Two additional issues were also considered. Although the major group in which these drugs would be used is front-line active duty personnel, there may also be dependents (including pregnant women and children) in some high-risk settings in whom the recommended therapies are contraindicated. And while all of the therapeutics discussed is FDA licensed, they are often not labeled for the prophylaxis and treatment of biowarfare agents. Such off-label use will require that potential recipients provide informed consent to be given the medication under an established protocol. However, the Board felt that labeling status should not be the determining factor if there was a clear best option based on the other criteria.

5. The Board made the following comments and recommendations:

a. **FOR THESE SIX THREAT AGENTS, ANTIBIOTIC ALTERNATIVES ARE LIMITED FOR BOTH PROPHYLAXIS AND TREATMENT. THE MAJOR ANTIBIOTICS UNDER CONSIDERATION BASED ON BROADNESS OF SPECTRUM AND EFFICACY ARE THE FLUOROQUINOLONES (SPECIFICALLY CIPROFLOXACIN) AND TETRACYCLINES (SPECIFICALLY DOXYCYCLINE). WHEN SUBJECT MATTER EXPERTS CONSIDERED THE CRITERIA ABOVE, THERE WAS LITTLE TO DIFFERENTIATE THESE TWO CLASSES IN TERMS OF A CLEAR BEST ALTERNATIVE. DOXYCYCLINE APPEARS TO HAVE A BROADER SPECTRUM, IN THAT IT IS CONSIDERED AN ALTERNATIVE FOR ALL SIX THREAT AGENTS, AND IS CONSIDERABLY LESS EXPENSIVE THAN ANY OF THE FLUOROQUINOLONES. HOWEVER, IT WAS CONSIDERED TO HAVE A GREATER INCIDENCE OF SIDE EFFECTS, AND WAS CONSIDERED MORE HARMFUL IN PREGNANT WOMEN AND CHILDREN. THESE DRUGS WERE FELT TO BE ROUGHLY EQUIVALENT WITH RESPECT TO THE OTHER CRITERIA (SHELF LIFE, EASE OF ADMINISTRATION, POTENTIAL FOR RESISTANCE, AND DRUG INTERACTIONS). REGARDLESS OF WHICH DRUG IS SELECTED AS THE FIRST CHOICE FOR ANY OF THESE DISEASES, THE OTHER MUST ALSO BE AVAILABLE AS A BACK-UP.**

b. **THE MDBM POLICY GROUP (WHICH ADDRESSED ONLY POST-EXPOSURE PROPHYLAXIS) SELECTED CIPROFLOXACIN AS THE DRUG OF CHOICE FOR ANTHRAX AND TULAREMIA WITH DOXYCYCLINE AS THE BACKUP, WHILE DOXYCYCLINE WAS THE FIRST CHOICE FOR PLAGUE WITH CIPROFLOXACIN AS THE BACKUP. DOXYCYCLINE (COMBINED WITH RIFAMPICIN FOR BRUCELLOSIS) WAS CONSIDERED THE FIRST LINE PROPHYLACTIC AGENT FOR GLANDERS, BRUCELLOSIS, AND Q FEVER. THE BOARD SUPPORTS THESE CHOICES.**

c. **FOR THERAPY, CIPROFLOXACIN IS ALSO THE DRUG OF CHOICE FOR ANTHRAX WITH DOXYCYCLINE AS THE BACKUP. FOR BOTH PLAGUE AND TULAREMIA, STREPTOMYCIN IS CONSIDERED THE TRADITIONAL THERAPEUTIC DRUG OF CHOICE, BUT BECAUSE OF THE ROUTE (INTRAMUSCULAR) AND FREQUENCY OF ADMINISTRATION, AND LIMITED SUPPLY, THIS DRUG POSES SIGNIFICANT LOGISTICAL CHALLENGES FOR LARGE SCALE USE IN COMPARISON TO OTHER AMINOGLYCOSIDES (SPECIFICALLY GENTAMICIN). THE BOARD RECOMMENDS THE SELECTION OF THIS DRUG FOR TREATMENT WITH CIPROFLOXACIN AS A THERAPEUTIC ALTERNATIVE. FOR Q FEVER AND BRUCELLOSIS THE THERAPEUTIC CHOICE IS DOXYCYCLINE (WITH RIFAMPICIN ADDED FOR BRUCELLOSIS) WHILE FOR GLANDERS THERAPY WOULD INCLUDE CEFTAZIDIME AND RIMETHOPRIM/ SULFAMETHOXAZOLE. SPECIFIC RECOMMENDATIONS ARE INCLUDED IN THE ATTACHED TABLE.**

d. **IT IS OUR UNDERSTANDING THAT THE MANUFACTURERS OF CIPROFLOXACIN ARE ENGAGED IN DISCUSSIONS WITH FDA TO DETERMINE THE REQUIREMENTS FOR CHANGING THE LABELING TO INCLUDE PROPHYLACTIC USE AGAINST THE MAJOR BIOWARFARE THREAT AGENTS. SHOULD A LABEL CHANGE OCCUR, IT WOULD BE AN ADDED INCENTIVE TO SELECT THIS DRUG OVER DOXYCYCLINE TO BECAUSE OF THE OFF-LABEL USE ISSUE. OF NOTE, NEWER FLUOROQUINOLONES HAVE THE ADVANTAGE OF ONCE DAILY ADMINISTRATION. ALTHOUGH DOSING FREQUENCY IS MORE OF AN ISSUE IN CIVILIAN SETTINGS, THE ADDED EASE OF ADMINISTRATION WOULD BE A STRONG CONSIDERATION FOR SELECTION OF ONE OF THESE AGENTS (I.E. LEVOFLOXACIN) IF BIOEQUIVALENCY AGAINST THE THREAT AGENTS COULD BE DETERMINED AND THE COST WAS NOT SIGNIFICANTLY DIFFERENT.**

e. SPECIFIC RECOMMENDATIONS*:

	POST-EXPOSURE PROPHYLAXIS		THERAPY	
Threat Agent	**1st Choice**	**2nd Choice**	**1st Choice**	**2nd Choice**
Anthrax	**Ciprofloxacin**	**Doxycycline**	**Ciprofloxacin**	**Doxycycline**
Plague	**Doxycycline**	**Ciprofloxacin**	**Gentamicin**	**Ciprofloxacin**
Tularemia	**Ciprofloxacin**	**Doxycycline**	**Gentamicin**	**Ciprofloxacin**
Glanders	**Doxycycline**		**Ceftazidime TMP/Sulfa**	
Brucellosis	**Doxycycline Rifampicin**		**Doxycycline Rifampicin**	
Q fever	**Doxycycline**		**Doxycycline**	

***Dosage and duration as per MBDM guidance**

6. The above comments and recommendations were unanimously approved by the Board.

7. The above comments and recommendations have been reviewed by the appropriate representatives from the CDC who also concur.

FOR THE ARMED FORCES EPIDEMIOLOGICAL BOARD:

F. MARC LAFORCE, M.D.
AFEB President

BENEDICT M. DINIEGA
Colonel, USA, MC
AFEB Executive Secretary

2 Encls
1. Question to Board
2. MBDM Recommendations

AFEB (15-1a) 00-9 03 August 2000
SUBJECT: Antibiotics Against Biowarfare Agents

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HEALTH AFFAIRS

MAR 13 2000

MEMORANDUM FOR THE ARMED FORCES EPIDEMIOLOGICAL BOARD

SUBJECT: Antibiotics Against Biowarfare Agents

The Armed Forces Epidemiological Board (AFEB) has been very helpful in the review and prioritization of biological threat agents facing our Armed Forces. In our continuing efforts to ensure that the most effective medical therapies are readily available for the military, we additionally require a review of antimicrobial drugs.

In light of the need for the Department of Defense to maintain a high level of readiness and to maintain adequate stockpiles of specific antibiotics, I request that the Armed Forces Epidemiological Board conduct a review of antibiotics approved by the Food and Drug Administration that may prove useful against certain infectious biological warfare agents. This review should involve appropriate consultation with Centers for Disease Control and Prevention (CDC) staff, as they will have very similar concerns regarding what is needed for the domestically-oriented national pharmaceutical stockpile for medical response to terrorism.

I ask the AFEB to provide recommendations to this office on the most appropriate antibiotics that would be indicated for the treatment of the primary bacterial and rickettsial agents on the biowarfare threat list. Of greatest concerns are the infectious agents causing anthrax, plague, tularemia, brucellosis, glanders, and Q fever. The recommendations should describe any precautions or contraindications associated with the administration of any antibiotics.

I request that you address this issue at your next AFEB meeting in May in concert with your periodic review of the threat list and provide your results within 60 days of your meeting.

RADM J. Jarrett Clinton, MD, MPH, USPHS
Deputy Assistant Secretary of Defense
(Health Operations Policy)