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DEPARTMENT OF THE ARMY
WALTER REED ARMY INSTITUTE OF RESEARCH
WALTER REED ARMY MEDICAL CENTER
WASHINGTON, D.C. 20307-5100



IN REPLY REFER TO:

SGRD-UWZ-H

7 December 1990

MEMORANDUM THRU Commander, USA Medical Research and Development
Command, Fort Detrick, Frederick, Maryland
21701-5012

FOR The Surgeon General, 5109 Leesburg Pike, Falls Church, VA
22041-3258

SUBJECT: Tri-Service Vaccine Task Force (Appendix A)

BACKGROUND:

1. Diarrheal diseases have always been significant military problems in Middle East campaigns (e.g. WWI, Gallipoli; WWII, El Alamein; Suez crisis, UK, 1956; Lebanon, USA, 1957 and 1983; Israeli Defense Force, 1966, 1972, 1983) and have been implicated as contributing determinants of victory (Rats, Lice and History, H. Zinsser, c 1939 Little-Brown, Co. Boston, MA). Diarrheal diseases have already proven problematic in Desert Shield and with the increasing likelihood of a continued U.S. presence, are destined to become an even greater problem (Appendix B). Furthermore, resistance to ciprofloxacin, the only currently effective antibiotic to treat shigellosis, is predicted to occur within 12-16 months (Appendix B).

2. Hepatitis A is transmitted by the fecal-oral route and follows the same epidemiologic pattern as diarrheal diseases. Hepatitis A was a significant problem for U.S. troops in the North African campaign in WWII and is a persistent problem for the Israeli Defense Force. Hence, our policy of prophylaxis with Immune Serum Globulin. However, this requires repeated injections every three months and is an inadequate long term strategy (Appendix C).

3. Post wounding sepsis in modern warfare has become a major cause of morbidity, mortality and cost. Hence, a USAMRDC mission has been to develop vaccines against the major causes of post wounding sepsis. Because of the difficulty in performing the appropriate human studies, the approach taken has been to first demonstrate efficacy by producing hyperimmune antisera and human monoclonal antibodies and then fashion the antigen into a vaccine. The individual vaccines are in various stages of development (Appendix D).


EDMUND C. TRAMONT, COL, MC

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4. Over the past 20 years, the USAMRDC has switched its emphasis from diseases of mobilization (i.e. vaccines to prevent meningococcal disease) to diseases of deployment (i.e. vaccines to prevent wound sepsis). However, a major impediment to the determination of product efficacy has been the lack of a true operational deployment scenario. Thus, we have the research requirement of determining true efficacy during times of actual deployment.

RECOMMENDATIONS:

1. Institute available IND Cholera vaccine immediately to prevent diarrhea due to LT enterotoxigenic E. coli and cholera (Appendix B).

8 mil

2. Institute available licensed Typhoid vaccine Ty21a immediately to prevent Typhoid Fever (Appendix B).

Wait for routine use, FEB.

3. Institute available IND Hepatitis A vaccine immediately to prevent Hepatitis A (Appendix C).

Perhaps pre-deployment, 2 doses after new data

4. Expand use of Centoxin for prophylaxis to all wounded personnel with abdominal, chest, burn (to include mustard gas) and head trauma (Appendix D).

5. Establish as high priority the institution of a "Manhattan-like project" to evaluate the above vaccines in a real operational setting and to develop specific vaccines for Shigella sonnei, STLT and ST enterotoxigenic E. coli, West Nile Fever, and post-wound infectious agents.

6. Create a Tri-Service Research Task Force to coordinate this high priority emergency endeavor and to provide expert advice and assistance on vaccines, etc. of benefit for Desert Shield to the Tri-Service Joint Technology Working Group for Infectious Disease under the ASBREM and to the USAMRDC for procurement of products.

7. Provide appropriate funding to accomplish this mission in a timely fashion.

EDMUND C. TRAMONT
COL, MC
ID Consultant, OTSG

Probably if available
2500, 1000
10 mil



REPORT TO
ATTENTION OF

~~CONFIDENTIAL~~ UNCLASSIFIED
DEPARTMENT OF THE ARMY
OFFICE OF THE SURGEON GENERAL
8109 LEEBURG PIKE
FALLS CHURCH, VA 22041-3288



SGPS-CP (340d)

MEMORANDUM FOR Commander, Medical Research and Development
Command, Fort Detrick, MD 21701-5012

SUBJECT: Tri-Service Vaccine Task Force

1. This is a tasking to establish a Tri-Service Vaccine Task Force with Army as the executive agent. I want MRDC to be my lead in this endeavor.

2. Background: Several vaccines and potential vaccines with specific relevance to Desert Shield have been identified by the TSG Consultant in Infectious Disease. They include:

- a. Enterotoxigenic E. Coli
- b. Typhoid 21 A
- c. Hepatitis A
- d. Centoxin (Monoclonal antibody)
- e. Shigellosis Sonii

3. Guidance:

a. The Task Force purpose is to evaluate the potential of the vaccines noted above, and any others that might come to light, for use in the Desert Shield Operation, and to provide appropriate recommendations through the Army Surgeon General to the Assistant Secretary of Defense for Health affairs.

b. The Task Force should be headed by a senior Army Physician with the academic stature to direct such an effort. I suggest COL Ed Tramont for this with your able staff in support. COL Tramont will, with the other services, be able to select quality tri-service representation.

c. Consideration should be given not only to the ability to produce the vaccine, but to the potential benefits balanced against costs both in dollars and in diversion of resources from other projects. The appropriate target population to be inoculated must be defined. The implications of fielding IND drugs should be clearly evaluated.

d. Consultation should be obtained whenever needed to ensure the military relevance of any program. It is on the basis of such data that the CENTCOM leadership will act upon a recommendation to vaccinate.

SGPS-CP (340d)

SUBJECT: Tri-Service Vaccine Task Force

e. Finally note that this effort should be accomplished within your budget or with minimal additional funding.

4. I would like this project to start immediately. The Task Force chairman should coordinate with the Air Force and Navy to provide a plan of attack which I can staff with the other Surgeons General and DOD Health Affairs. Provide this plan to me by 7 December 90.

FRANK F. LEDFORD, JR.
Lieutenant General
The Surgeon General



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Appendix B

IN REPLY REFER TO:

SGRD-UWF-J

7 December 1990

MEMORANDUM FOR Head, Tri-Service Vaccine Task Force

SUBJECT: Vaccines to Prevent Diarrhea and Typhoid Fever in Operation Desert Shield

1. THE DIARRHEA PROBLEM. To date, diarrhea has been the most common medical problem encountered during Desert Shield. Between 2-5 percent of troops in Desert Shield visit health care facilities every week for diarrhea. However, only 20% of persons are presenting themselves for treatment. Thus, about 20,000 cases per week are occurring.
2. 55% (11,000 cases/wk) of diarrhea are caused by enterotoxigenic Escherichia coli (ETEC), 20% (4,000 cases/wk) are caused by Shigella species, and the remaining 25% are unknown. 69% of ETEC diarrhea diagnosed thus far were caused by ETEC which produce the heat-labile toxin (LT) and 31% were caused by ETEC producing the heat-stable toxin (ST). The problem will become worse as more new forces are deployed and the present cool weather subsides. Over 90% of the Shigella isolated thus far are Shigella sonnei; but other serotypes, most commonly S. flexneri, are endemic in the area and are likely to become a significant problem. Shigella from this area are resistant to all commonly used antibiotics except ciprofloxacin. Resistance to this drug has been documented in Africa and will result in Desert Shield from widespread use of this antibiotic. Although no Vibrio cholerae have been isolated in a U.S. service member thus far, cholera has been reported in this area and has at times been epidemic. Salmonella typhoid (typhoid fever) is also endemic in this region and recent reports from Bahrain indicate that strains in the region are often resistant to antibiotics commonly used for treatment of typhoid fever. Presently used parenteral vaccines are protective but give unsatisfactory high incidence of side effects.
3. PREVENTION OF CHOLERA. A safe, oral cholera vaccine tested in Bangladesh in over 25,000 children and young adults provided highly significant protection against cholera and was completely safe (80% protection over 6 months, 60% protection over 12 months). This oral vaccine afforded more protection against cholera and for longer periods of time than the parenteral cholera vaccine used previously.

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SUBJECT: Vaccines to Prevent Diarrhea and Typhoid Fever in Operation Desert Shield

4. PREVENTION OF ETEC INFECTIONS. In addition to providing protection against cholera, the oral cholera vaccine also prevented LT and LTST ETEC infections because they produce a very similar enterotoxin as cholera. In the first three months following vaccination in the Bangladesh trial, there was 67% efficacy in preventing ETEC caused by either LT or LTST producing ETEC, ($p < 0.01$). No protection was found against infection caused by ST-producing ETEC. The oral cholera vaccine also protected western travelers from LT ETEC. In a recently completed study, 615 Finnish tourists received 2 doses of the oral cholera vaccine 2 weeks apart before traveling to Morocco. When compared to a control group, the oral cholera vaccine prevented 69% of LT and LTST infections. These two studies indicate that the oral cholera vaccine could offer significant protection against ETEC infections among troops in the Persian Gulf.

5. AVAILABILITY OF THE ORAL CHOLERA/ETEC VACCINE. The oral cholera vaccine that was used in these two field trials was produced by Institute Merieux (France) and is currently under IND in the U.S.. The main problem with this vaccine as it was originally formulated was cost. However, this problem has been overcome using recombinant technology. The Swedish National Bacteriological Laboratory (SNBL) has expressed a willingness to provide the oral cholera vaccine to the U.S. military. Estimated cost: \$8.00 per dose. Delivery: 3-4 months.

6. DEVELOPMENT OF AN IMPROVED ETEC VACCINE. It is possible to increase the efficacy of the oral cholera vaccine by substituting killed whole ETEC organisms for Virbro cholera. This vaccine has been shown to be safe and immunogenic when tested in humans in Sweden. This vaccine has the advantages over the oral cholera vaccine of protecting against ST ETEC strains and producing a longer lasting immunity.

7. DEVELOPMENT OF SHIGELLA VACCINES. There are three scientific approaches which could lead to an effective vaccine within 6-12 months. These are (a) an oral E. coli hybrid effective against either S. sonnei or S. flexneri or both (WRAIR), (b) an attenuated S. sonnei vaccine (University of Maryland and Sweden), and (c) a parenteral conjugate vaccine (NIH).

8. NEW TYPHOID VACCINES. Two new typhoid vaccines have been shown to be safe, immunogenic and protective in clinical trials. These are: 1) an attenuated strain of Salmonella typhi, Ty21a, used as a live oral vaccine; and 2) the purified polysaccharide capsular antigen of S. typhi, Vi, administered as a parenteral vaccine. Ty21a is now licensed and has been extensively tested since 1978

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in field trials in Egypt, Chile, and Indonesia. In trials funded by the USAMRDC in Chile, this vaccine gave 66% protection for at least 5 years when 3 enteric coated capsules were given and 4 doses was shown to be significantly better than 3 doses, $p < 0.002$. This vaccine has now been given to over 100,000 persons without side effects. This vaccine will cost the U.S. military \$ 2.30 for the recommended 4-dose regimen and is available for immediate purchase. Although no comparative trials of the killed parenteral and the oral vaccines have been done, data is sufficiently strong to suggest that the oral vaccine is at least as effective as the killed parenteral vaccine.

RECOMMENDATIONS:

1. DIARRHEA INITIATIVE. The effective prevention and treatment of diarrheal disease is a very high priority during Operation Desert Shield. There are many causes of diarrhea of which ETEC and Shigella are the most prominent causes. Constant surveillance of disease rates, etiologies, and antimicrobial susceptibility patterns is essential for the most rational way to plan prevention strategies.
2. ETEC/CHOLERA PREVENTION. The oral cholera vaccine is completely safe and has provided significant protection against LT ETEC and cholera. This oral cholera vaccine should be purchased to vaccinate all U.S. military personnel in the Persian Gulf region. This would require 1,000,000 doses (2 doses for 500,000 personnel). Vaccine efficacy field trials should be planned where feasible.
3. ETEC VACCINE. We anticipate that the B subunit/whole cell ETEC vaccine will be superior to the oral cholera vaccine for prevention of ETEC. The oral ETEC vaccine should be developed as rapidly as possible. This requires purchase of a test lot from Sweden to test for safety and immunogenicity in military personnel stationed in the U.S.. Once efficacy has been demonstrated by challenging vaccinated volunteers, we will substitute (or add) this vaccine to the cholera vaccine.
4. ORAL SHIGELLA VACCINES. Rapid development of an E. coli/S. sonnei hybrid vaccine entails scheduling of production facilities, expedited review of protocols, scheduling of vaccine testing centers, and informing the FDA that this project has high priority. Following inpatient safety and efficacy studies, large scale outpatient safety testing could begin in late March with deployment to Desert Shield forces by mid-April.

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5. SHIGELLA POLYSACCHARIDE VACCINES. Rapid development of this vaccine for use in Desert Shield will entail expedited reviews and signing of a CRDA between USMRDC and the NIH.

6. TYPHOID VACCINE. Ty21a should be bought in sufficient quantities to be used in all unimmunized troops deployed in Operation Desert Shield. The oral vaccine should replace the killed vaccine as the vaccine of choice for prevention of typhoid fever in the U.S. military.

POC: LTC David Taylor
AV 291-3658