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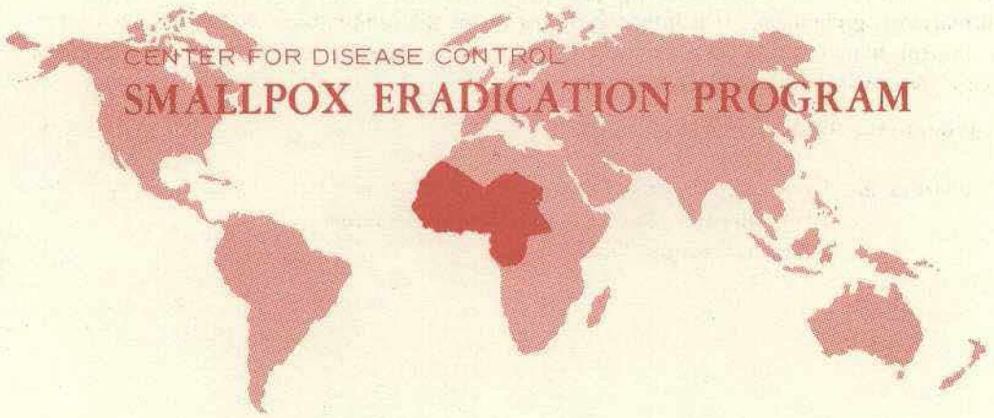
June 1971



CENTER FOR DISEASE CONTROL

SMALLPOX ERADICATION PROGRAM

THE SEP REPORT

CHOLERA IN WEST AFRICA

Comparison of the Intradermal and Subcutaneous
Routes of Cholera Vaccine Administration
(Preliminary Report)

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

PUBLIC HEALTH SERVICE

PREFACE

Summarized in this report is information pertaining to smallpox eradication and information received from Ministries of Health investigators, WHO, PAHO and other pertinent sources. Much of the information is preliminary. It is intended primarily for the use of those with responsibility for disease control activities. Anyone desiring to quote this report should contact the original investigator for confirmation and interpretation.

Contributions to the Report are most welcome.

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CHOLERA IN WEST AFRICA

I. OVERVIEW

Since El Tor cholera, Ogawa serotype, was introduced into Guinea in August of 1970, cholera disease has been reported from 13 West African countries. Cholera had not been recognized in West Africa since 1894, nor had its known spread been so extensive.[1] The countries which have officially reported cholera are Guinea, Sierra Leone, Liberia, Mali, Ivory Coast, Ghana, Upper Volta, Togo, Dahomey, Niger, Nigeria, Cameroon and Chad. The progress of this disease as it moved from west to east can be seen in Figure I. (Data not yet available from Chad.) Its spread followed basically one of two routes, the coast bordering the Gulf of Guinea or the Niger River. Thus, water (although in a different sense than the common source water-borne outbreak described by Snow[2] at the Broadstreet Pump in London in 1854) played a major role in the dissemination of cholera. In both of these areas, water serves as the major transportation and communication link within and between countries. In the coastal area, the fishermen and traders who ply the coast without respect to international borders gradually brought the disease eastward approximately 1,750 miles over a five month period. Along the Niger River, the mode of spread by fishermen and travelers was similar, the rate of spread faster and the effect the same. Once cholera was introduced into a given region or village, multiple factors such as the availability of a safe water supply, the cooking practices, and the level of personal hygiene and community sanitation influenced the effect of the importation.

II. ATTACK RATES

The total number of people infected with the disease will never be accurately known. Present official totals from 12 countries indicate approximately 24,075 clinical cases with 3,445 deaths. Based on the report of Bart, et al,[3] who found 36 sub-clinical infections for every clinical case of El Tor cholera, it can be estimated that there have been at least 870,000 cholera infections in West Africa since August 1970. Reported cholera cases, deaths, attack rates, and case fatality ratios are presented by country in Table I. Country-wide attack rates are difficult to interpret because a given area within a country may have a very high attack rate although the country itself would appear to have been relatively unaffected by the disease. For example, one country with an attack rate of less than 0.5 per 1000 persons had an area where the

[1]Politzer, R., Cholera, 1959, WHO Tech. Series, No. 43, Geneva, Switzerland.
[2]Snow on Cholera, Commonwealth Fund, New York, 1936.
[3]Bart, K.J., et al, J. Inf. Dis. 121:S17, 1970.

cholera mortality rate was 10.5/1000. The attack rate for the coastal region[4] is 1.46 reported cases per 1,000 persons. In the subsaharan savannah belt[5] the attack rate is approximately 0.64 reported cases per 1,000 persons.

III. MORTALITY AND TREATMENT

The mean case-fatality ratio shown in Table I is 14 deaths per 100 cases with a range of 3 to 45. Countries which were well prepared for the disease through education of health personnel in cholera treatment, preparation and distribution of treatment supplies, and good laboratory supported surveillance, were able to keep their case-fatality ratio to a minimum of about 5 per 100. They have demonstrated that disease management in Africa can result in very low case-fatality ratios similar to those reported from the SEATO-Pakistan Cholera Research Laboratory in Dacca and the Johns Hopkins University Center for Medical Research and Training, School of Tropical Medicine, Calcutta, India,[6] and other treatment centers.

IV. SPECIAL EPIDEMIOLOGIC SITUATIONS

A. Rivers

Although the coastal area and the Niger River have been the main avenues of disease spread, within inland areas smaller fresh water rivers used as the primary source for water have carried the disease downstream from infected villages to previously uninfected ones. Along brackish coastal rivers not used for drinking water, the disease has spread upstream via contaminated food items or infected people.

B. Markets

Markets, also, are an excellent source of transmission through contamination of food being handled by infected people in local markets. A good example is fish, particularly dried fish which become contaminated after the drying process is completed at the time of sale by the local vendors. The freshening of market vegetables with water, a common practice in West Africa, led to an outbreak in Israel when contaminated water was used.[7] The market in Mopti was the first major source of dissemination of cholera along the Niger River in Mali.

[4]Southern Parts of Ivory Coast, Ghana, Togo, Dahomey, Cameroon.
[5]Portions of Mali, Upper Volta, Niger (See Table I for specific areas included).
[6]Carpenter, C.C.J., et al, 1966, Bull. Johns Hopkins Hosp., 118: 174; Gordon, R., et al, 1964, PakMed.J. 8:10; Wallace, C.K., et al, 1968, Bull. WHO 39, 239.
[7]Langmuir, A.D., Epi-AID Memo 71-36-2.

C. Cholera Illness and Death

Because of their importance in the West African situation, the role played by the sick and dead person in the transmission of cholera should be noted. People who become ill often return to their home village bringing with them their disease. Such people have been documented to be the source of introduction of cholera into previously uninfected villages. In some cultures, if the person should die, the funeral preparations are conducive to disease transmission. The body may be washed and handled quite extensively by the mourning immediate family members. Although burial is prompt, the ceremony which accompanies it attracts many relatives and friends from various distances. In some societies ceremonies will last a number of days and be repeated several times during the months after death. The clothes or bedding of the deceased may be utilized during the ceremony, and great amounts of food, often uncooked, are prepared and shared by all people. There are frequent chances for common source food- and water-borne dissemination of the disease under such conditions.

V. VACCINATION

The SEATO-Pakistan Laboratory has calculated for Pakistan that it is cheaper and more productive to provide diarrhea treatment centers than to carry out vaccination programs.[8] Some countries in West Africa have mounted inexpensive vaccination programs by utilizing smallpox-measles teams and have shown that in particular areas vaccination may be one of the appropriate methods of combatting the disease. Each country or region should evaluate its own particular situation by attempting to predict the amount of disease and anticipating the relative cost of prevention and the relative cost of treatment. In areas which have the characteristics of being readily accessible, expecting a large amount of disease, and for which personnel or other treatment facilities are marginal or unavailable, vaccination may be a very viable choice. In other areas extensive treatment capability, safe water and food sources, geographic inaccessibility, and the importance of other vaccination campaigns may make vaccination inappropriate and the role of diarrhea treatment centers more important. Experience has shown that such centers established in West Africa can achieve the success which has previously been demonstrated in Pakistan and India and that effective adequate treatment is preferred over vaccination because of lower mortality rates.

[8]Sommer, A., Personal Communication.

VI. FUTURE - PREDICTIONS AND PLANNING

The future expectations and plans for cholera have a direct relationship to the future planning of health activities in West Africa. There has been disruption of planned maintenance and other smallpox-measles activities in many countries in response to the threat and actuality of cholera disease. Many countries are now witnessing large increases in the number of measles cases. This might have been averted by appropriate mass vaccination against measles in lieu of the cholera activities.

The persistence of cholera disease in certain areas; for example, Central, Accra and Eastern Regions of Ghana for four months with some evidence of reinfection of certain persons and localities, raises the question of cholera becoming endemic with possible epidemic spread from these foci at various times under certain conditions. Disturbingly, the hardiness of the El Tor biotype and the large number of subclinical infections caused by the organism not only increase the chance of spread of disease, but have allowed this biotype to compete successfully with other bacteria in the environment. Countries such as the Philippines, Thailand and Indonesia which had not been affected with El Tor cholera prior to the Seventh Pandemic became affected from 1961 to 1963 and they are still reporting disease. Thus, West African countries should expect to have disease for a number of years, perhaps even a decade.

Cholera is known to reach epidemic proportions in Southeast Asia at various times of the year, in either the wet or dry season, depending on the locality and the people involved. The major effect may not be the environmental results of the weather, but the way weather affects the activities of people. As the rains begin in West Africa in May and June, communication between people will decrease as the travel conditions deteriorate, and in those areas with a predominant agricultural sector people will move to widely scattered farms. This will reduce the mixing of people and will decrease the possibility of disease transmission. For these reasons, we anticipate that cholera will continue to decrease over the next few months. Next fall, with an increase in travel, a regathering of farmers in their villages, and the waning of naturally acquired and vaccination immunity, cholera will again be a potential threat.

Thus, the need for surveillance is of paramount importance. Because of the explosive nature of the disease, the origin and magnitude of any new foci which develop must be identified quickly.

Efforts should be made to improve laboratory competence in this direction through adequate training and distribution of transport media. Medical personnel not trained or experienced in treatment of cholera should receive instruction. Contingency plans should be made for establishment of treatment centers and/or vaccination programs, as appropriate, to avoid disruption of on-going programs. The possibility of adding cholera vaccine as an additional antigen to planned programs should be considered. Health education concerning the route of transmission of the disease should continue. Continued pressure must be maintained for the provision of safe water for all people. Areas of critically high population density, including all of the large cities, deserve special consideration and should be observed closely. It is these areas in which disease will be able to continue at a low level of transmission and from which future epidemics may develop.

TABLE 1

Reported Cholera Disease in West Africa

Country	Month of Peak No. of Cases	Pop. at Highest Risk (Millions)	No. of Cases	Attack Rate/ 1,000	No. of Deaths	Case Fatality Ratio
Guinea	Aug	3.9[1]	2,000[a]	0.51	60	3
Sierra Leone	Dec	2.5[1]	340[b]	0.14	47	14
Liberia	Nov	1.1[1]	201[c]	0.19	45	22
Ivory Coast	Nov-Dec	1.5[2]	1,500[d]	1.00	120	8
Mali	Nov-Dec	3.9[3]	3,491[e]	0.89	1,335	38
Ghana	Jan-Feb	7.0[4]	8,234[f]	1.17	417	5
(Southern Ghana		4.8[5]	8,143[f]	1.70	412	5)
Niger	Jan	3.5[6]	1,913[g]	0.55	336	18
Upper Volta	Jan-Feb	1.17[7]	222[h]	0.19	102	45
Togo	Dec-Jan	0.46[8]	437[i]	0.95	25	6
Dahomey	Jan	1.18[9]	1,685[j]	1.43	251	16
Nigeria	Jan-Apr	NA	3,709[k]	NA	647	17
Cameroon	Feb-Mar	.36[10]	343[l]	0.95	60	17
TOTAL*		26.5	20,366	0.77	2,798	14

[1]Total population used as demonimator because whole country infected or geographic extent of disease unclear
[2]Southeast Ivory Coast only
[3]Excluding Keyes Region
[4]Excluding Upper and Northern Regions
[5]Excluding Upper, Northern, Brong-Ahafo and Ashanti Regions
[6]Excluding Agadez and Diffa Regions
[7]Dori, Ouahigouya and Dedougou Sectors only
[8]Anecho, Vogan, Lome and Tabligbo Circumscriptions only
[9]South, Southeast and Southwest Departments only
[10]Wouri Department only

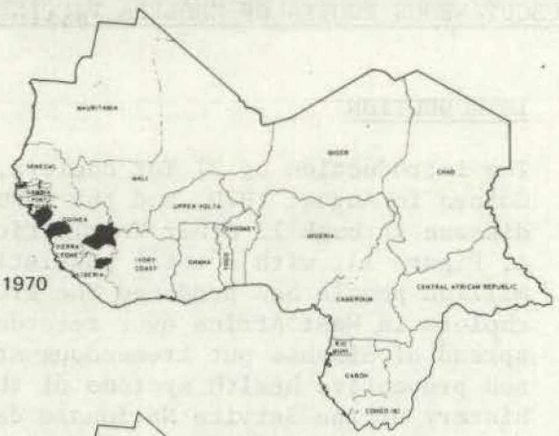
NA - Not Available

[a]Reported for August 1970 (WER 45,377, 4Sep70)
[b]Reported to March 20, 1971
[c]Reported to February 1, 1971
[d]Reported to March 1, 1971
[e]Reported to April 17, 1971

*Excluding Nigeria

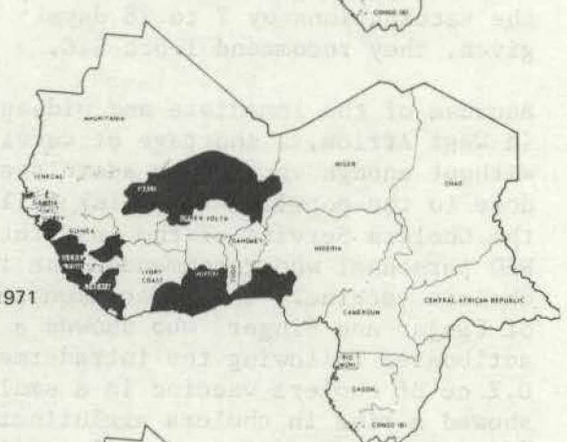
[f]Reported to mid-March 1971
[g]Reported to April 16, 1971
[h]Reported to April 5, 1971
[i]Reported to April 24, 1971
[j]Reported to March 13, 1971
[k]Reported to April 3, 1971
[l]Reported to March 20, 1971

COUNTRIES WHICH HAVE REPORTED CHOLERA
WEST AND CENTRAL AFRICA– 1970 AND 1971



AS OF SEPTEMBER 30, 1970

AS OF NOVEMBER 30, 1970



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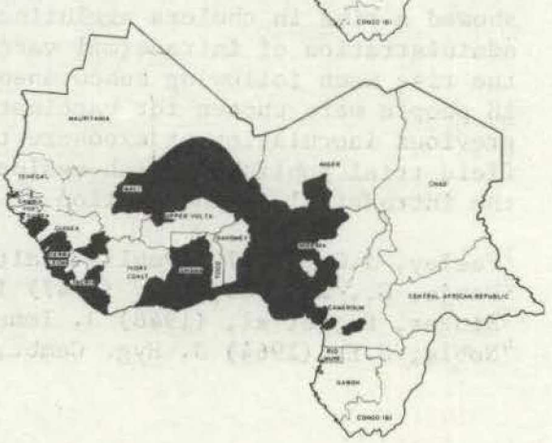

AS OF MARCH 31, 1971

PRELIMINARY REPORT OF COMPARISON OF THE INTRADERMAL AND SUBCUTANEOUS ROUTES OF CHOLERA VACCINE ADMINISTRATION

I. INTRODUCTION

The introduction of El Tor cholera, Ogawa serotype, into Guinea in August 1970, and the subsequent spread of the disease through 13 other West African countries, (Section A, Figure 1), with a total population of approximately 100 million people has produced the widest involvement of cholera in West Africa ever recorded. This relentless spread of disease put tremendous strain on the therapeutic and preventive health systems of the area. Because of the history of the Service Nationale des Grandes Endémies in Francophone West Africa, the Medical Field Units in Anglophone West Africa, the more recent Smallpox/Measles Program, all of which have relied heavily on immunizations as a way of preventing disease, the governments and people of West Africa looked to mass immunization to prevent cholera disease and its spread.

The USPHS Advisory Committee on Vaccinations recommends an adult cholera immunization schedule of a primary dose of 0.5cc subcutaneously or intramuscularly followed four weeks later by a 1.0cc dose subcutaneously or intramuscularly. The latest World Health Organization recommendation suggests separating the vaccinations by 7 to 28 days.[1] If only one dose can be given, they recommend 1.0cc S.C.

Because of the immediate and widespread desire for vaccination in West Africa, a shortage of vaccine developed. Governments without enough vaccine to administer the standard recommended dose to the population at risk followed the suggestions of the Cholera Service of the Institut Pasteur, Paris, and certain WHO personnel who recommended one intradermal dose of 0.2cc of cholera vaccine. These recommendations were based on the work of Panja[2] and Singer[3] who showed a rise in cholera agglutinating antibodies following the intradermal administration of 0.1 and 0.2 cc of cholera vaccine in a small group of people. Noble[4] showed a rise in cholera agglutinating antibodies following administration of intradermal vaccine which was comparable to the rise seen following subcutaneous vaccination. However, only 18 people were chosen for vaccination of whom only ten had no previous inoculation or exposure to cholera. There has been no field trial published which evaluates the protective effect of the intradermal administration of cholera vaccine.

[1]Feeley, J.C., (1970) Public Health Papers, No. 40:87.
[2]Panja, G., and Das, N.W. (1947) Ind. Jour. Med. Res. 35:3.
[3]Singer, E., et al, (1948) J. Immunol. 60:101.
[4]Noble, J.E. (1964) J. Hyg. Camb., 62:11.

Vaccine field trials have demonstrated the efficacy of subcutaneously administered cholera vaccine, although the protection is incomplete, 46-80%, and short lived (3-6 months).[5,6,7,8] Mosley, et al,[9] have shown the predictive value of the vibriocidal antibody titer in evaluation of cholera vaccine and have demonstrated an inverse relationship between the cholera case rate and the vibriocidal titer. Specifically, there is 44% reduction in case rate for every doubling of vibriocidal titer.

In an effort to ascertain the relative effectiveness of the two different modes of cholera vaccine administration, a trial was carried out to compare the vibriocidal antibody response to the intradermal and subcutaneous routes of cholera vaccine administration.

II. MATERIALS AND METHODS

A. Vaccine

Freeze-dried cholera vaccine prepared after formalin inactivation of monovalent Ogawa and Inaba cultures was used. It was manufactured by Merck, Sharpe & Dohme, and was made available by Division of Biological Standards, National Institutes of Health, Bethesda, Maryland, under DBS-IND 313. The vaccine was reconstituted using sterile isotonic 0.02 molar phosphate buffered saline, pH 7.2 containing 0.25% phenol, to a final concentration of 4×10^8 organisms of each strain per cc. Vaccines used in this study were lot 4446G (Ogawa) and lot 4445G (Inaba). The vaccines were diluted the night prior to vaccination, were promptly refrigerated, and remained refrigerated until the time of vaccine administration.

The dT and DPT vaccines were commercially manufactured vaccines (Wyeth).

B. Vaccine Administration

The vaccine was administered to the deltoid region of the upper left arm, using the Ped-O-Jet (Scientific Equipment Manufacturing Company, Lodi, New Jersey). Intradermal vaccine administration was accomplished using the intradermal (smallpox) nozzle. The subcutaneous vaccine was administered using the subcutaneous (measles) nozzle.

[5]Oseasohn, R.O., et al, (1965) Lancet, 1:450.
[6]Benenson, A.S., et al, (1968b) Bull. Wld. Hlth. Org. 38:359.
[7]Mosley, W.H., et al, (1969) Bull. Wld. Hlth. Org. 40:177.
[8]Mosley, W.H., et al, (1970) J. Inf. Dis. 121:S1.
[9]Mosley, W.H., et al, Op.Cit., 1969.

C. Subjects

The subjects for the study came from Ouagadougou Sector, Upper Volta, who were residents at the Petit Seminaire, Pabre, and the College Protestant, Loumbila. All were from 14 to 20 years of age. All of the participants were accepted in the order they appeared for the study and then assigned to an appropriate vaccination section based on previously selected random numbers.

D. Vaccination Schedule

All vaccinations were given during weeks 0 and 4 of the study, as indicated in Table I.

E. The Collection of Specimens

Finger tip blood specimens were collected during week 0 just prior to the first cholera vaccination. Subsequent specimens were or will be obtained during weeks 2, 6, 10, and 16. In all instances, paired specimens were obtained prior to and following the appropriate vaccinations.

The finger tip blood specimens were collected in 0.05 ml capillary tubes (Microcaps, Drummond Scientific Company, Bromall, Pa.), and they were immediately placed into 0.45 ml of sterile saline in a screw capped vial. These vials were placed in a field cold box and were transported to Ouagadougou at the end of each morning where they were placed in a refrigerator, centrifuged, and separated within 24 hours. Separation was achieved through use of a standard laboratory centrifuge. The serum which was considered to be in a 1:10 dilution for analysis of titers was then frozen at -20°C, and was transported frozen to CDC for vibriocidal titer determination. Vibriocidal titers were measured at CDC using the micro technique of Beneson, et al.[10]

III. RESULTS

A portion of the results of the study to date are shown in Tables 2 and 3 and in Figure 2. We arbitrarily defined seroconversion to be a four-fold or greater rise in antibody titer following the administration of cholera vaccine. The intradermal section has a percent seroconversion of 97.6 at two weeks. All of the people in the subcutaneous section showed seroconversion. No person in the control group demonstrated a significant change in antibody titer during the same period.

[10]Benenson, A. S., et al, (1968a) Bull. Wld. Hlth. Org., 38:277.

The magnitude of the post vaccination vibriocidal titers are shown in Table 3 and Figure 2. The reciprocal geometric mean titer for the intradermal section at two weeks was 951. The value for the subcutaneous section was 2609. At six weeks the respective values were 384 and 1305. The control section had titers of 34 and 37.5.

IV. DISCUSSION

The very high rate of seroconversion and the high level of the GMT found in this study population are comparable to that achieved at CDC in 1968 when EIS officers were vaccinated subcutaneously with the same vaccine. Thus, Africans with a generally lower standard of health and greater possibility of inter-current diseases appear to respond similarly to young American adults.[11]

Comparison of the geometric mean titers between sections provides an indication of the relative protective effect of the two methods of vaccine administration. Dr. Mosley has pointed out that we can expect approximately 50% decrease in the case rate for a given population for every doubling of the vibriocidal titer. Based on this information, we can predict a 95 and 98% protection during week 2 for sections B and D respectively. During week 6 the protection would be 89 and 97%. Although these predicted rates of protection are higher than those generally reported, we should remember that these are for only the first six weeks following vaccination. The measured protection of 46-80% reported from Pakistan cover periods up to 3-6 months following vaccination. Therefore, we can expect our GMT's to decrease with time, and the overall protection afforded by the vaccine to be lower than indicated presently.

Verway[12] has shown that the decay of the plots of GMT against time are similar for a 200-fold range of cholera vaccine antigen potency and for different subcutaneous vaccination schedules. We might therefore be able to assume that there will continue to be an approximate three-fold difference between the GMT's of sections B and D. While the differences in predicted protection at two and six weeks are not significantly different, the extrapolated protection at 10 weeks would be 76 and 94% for sections B and D. Thus, we may see a greater protection resulting from the subcutaneous vaccination after 2 1/2 months. However, this is speculation, and we will have to wait for the data.

[11]Gangarosa, E. J., Unpublished Data.
[12]Verway, W. F., et al, (1969) Texas Reports on Biology and Medicine 27:Supplement 1, 243.

In summary, we can say at present, that the intradermal administration of cholera vaccine gives a predicted protection similar to that of the subcutaneous vaccine for a period of at least six weeks. The actual protection, however, can only be measured by the appropriate clinical trial in an area experiencing cholera disease.

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TABLE 1

Cholera Vaccine Study
Upper Volta

Vaccination and Serum Collection Schedule

Section		B	D	E
Week	0	Blood CV 0.2cc I.D.	Blood CV 1.00cc S.C.	Blood dT 0.5cc S.C.
"	2	Blood	Blood	Blood
"	4	dT 0.5cc S.C.	dT 0.5cc S.C.	dT 0.5cc S.C.
"	6	Blood	Blood	Blood
"	10	Blood	Blood	Blood
"	16	Blood	Blood	Blood

TABLE 2

Cholera Vaccine Study
Upper Volta

Percent Seroconversion ($\geq$ 4 Fold Rise In Vibriocidal Antibody Titer) Two Weeks Following Cholera Vaccination

Section	B	D	E
Vaccine, Dose & Route	CV 0.2cc I.D.	CV 1.0cc S.C.	dT 0.5cc S.C.
Number of Subjects	42	37	22
Percent Seroconversion Ogawa	97.6	100	0
Percent Seroconversion Inaba	90.4	97.3	0

Sections B and D not significantly different at 0.05 level

TABLE 3

Cholera Vaccine Study
Upper Volta

Reciprocal Geometric Mean Titers
Against Ogawa Serotype

Section		B	D	E
Week	0	24.0	22.3	28.3
"	2	951.0	2609	34.0
"	6	383.7	1305	37.5

TABLE 4

Cholera Vaccine Study
Upper Volta

Estimated Percent Reduction in Case Rate
Following Intradermal and Subcutaneous Cholera Vaccination

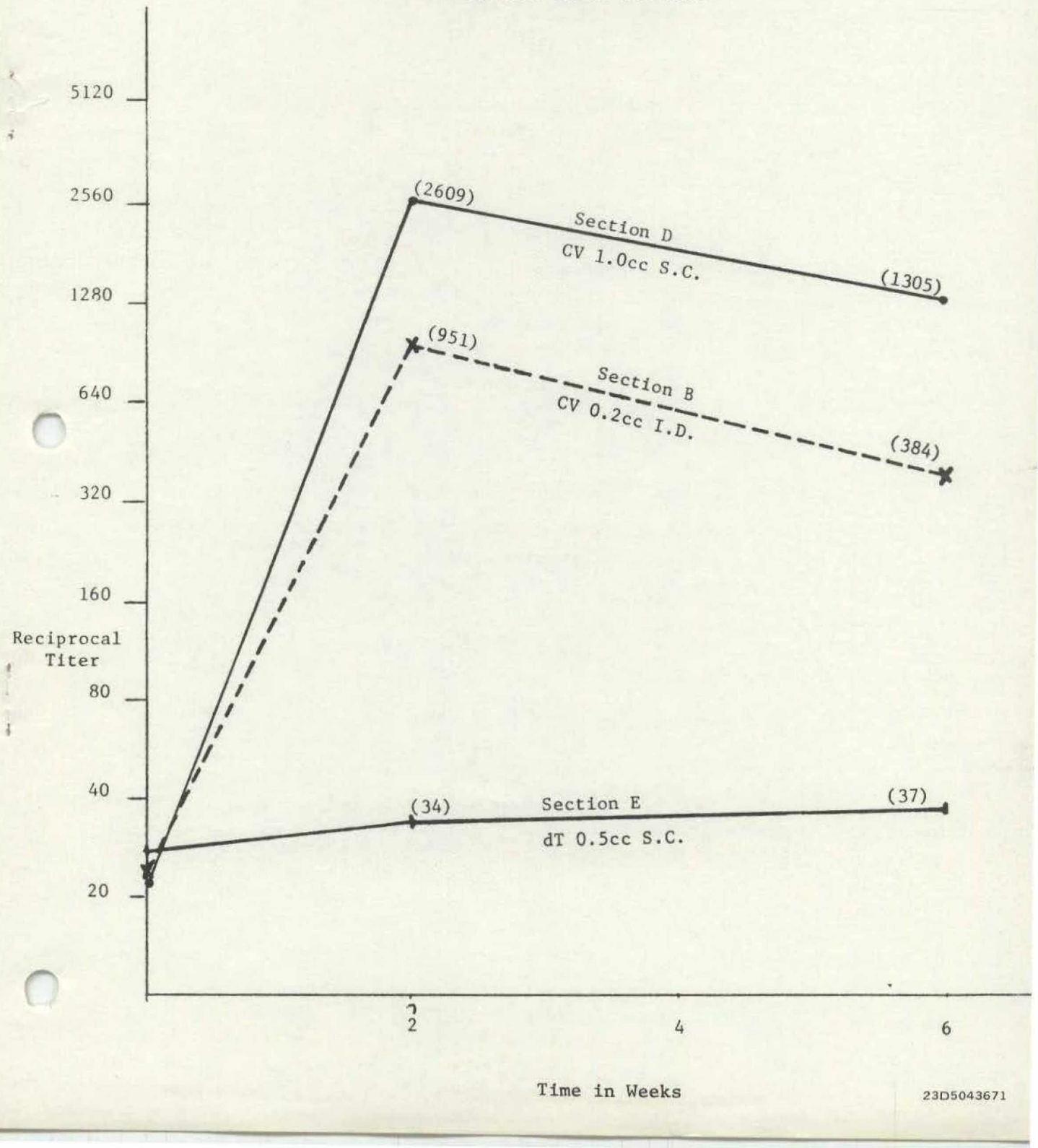
Section		B	D	E
Week	2	95	98	0
"	6	89	97	0
"	10*	76	94	0

*Extrapolated

Figure 2

CHOLERA VACCINE STUDY
Upper Volta

Reciprocal Geometric Mean Titers
Against Ogawa Serotype



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