Attachment 1.
(FACE SHEET)

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Date 8/3/92. 30/3/92.

Principal Investigator Dr M.A. Salam

Trainee Investigator (if any) To be recruited.

Application No. 92-008 (Revised)

Supporting Agency (if Non-ICDDR,B)

Title of Study "Randomized double-blind study of efficacy of cefixime in the treatment of shigellosis"

Project status:
(✓) New Study
( ) Continuation with change
( ) No change (do not fill out rest of form)

Circle the appropriate answer to each of the following (If Not Applicable write NA).

1. Source of Population:
   (a) Ill subjects (Yes) No
   (b) Non-ill subjects Yes (No)
   (c) Minors or persons under guardianship Yes (No)
2. Does the study involve:
   (a) Physical risks to the subjects Yes (No)
   (b) Social Risks Yes (No)
   (c) Psychological risks to subjects Yes (No)
   (d) Discomfort to subjects (Yes) No
   (e) Invasion of privacy Yes (No)
   (f) Disclosure of information damaging to subject or others Yes (No)
3. Does the study involve:
   (a) Use of records, (hospital, medical, death, birth or other) (Yes) No
   (b) Use of fetal tissue or abortus Yes (No)
   (c) Use of organs or body fluids (Yes) No
4. Are subjects clearly informed about:
   (a) Nature and purposes of study (Yes) No
   (b) Procedures to be followed including alternatives used (Yes) No
   (c) Physical risks (Yes) No
   (d) Sensitive questions (Yes) No
   (e) Benefits to be derived (Yes) No
   (f) Right to refuse to participate or to withdraw from study (Yes) No
   (g) Confidential handling of data (Yes) No
   (h) Compensation &/or treatment where there are risks or privacy is involved in any particular procedure (Yes) No
5. Will signed consent form be required:
   (a) From subjects (Yes) No
   (b) From parent or guardian (if subjects are minors) Yes (No)
6. Will precautions be taken to protect anonymity of subjects (Yes) No
7. Check documents being submitted herewith to Committee:
   ___ Umbrella proposal - Initially submit an overview (all other requirements will be submitted with individual studies).
   ✓ Protocol (Required)
   ✓ Abstract Summary (Required)
   ✓ Statement given or read to subjects on nature of study, risks, types of questions to be asked, and right to refuse to participate or withdraw (Required)
   ✓ Informed consent form for subjects
   X Informed consent form for parent or guardian
   ✓ Procedure for maintaining confidentiality
   ✓ Questionnaire or interview schedule *

* If the final instrument is not completed prior to review, the following information should be included in the abstract summary:
   1. A description of the areas to be covered in the questionnaire or interview which could be considered either sensitive or which would constitute an invasion of privacy.
   2. Examples of the type of specific questions to be asked in the sensitive areas.
   3. An indication as to when the questionnaire will be presented to the Cttee. for review.

We agree to obtain approval of the Ethical Review Committee for any changes involving the rights and welfare of subjects before making such change.

Principal Investigator

A-031958

Trainee

RESEARCH PROTOCOL

1.	TITLE	: RANDOMIZED DOUBLE-BLINDED STUDY OF EFFICACY OF CEFIXIME IN THE TREATMENT OF SHIGELLOSIS.
2.	PRINCIPAL INVESTIGATOR	: M. A. SALAM, M.B.B.S.
	CO-INVESTIGATOR	: WASIF ALI KHAN, M.B.B.S.
	CONSULTANT	: MICHAEL L. BENNISH, M.D.
	TRAINEE RESEARCH MEDICAL OFFICER	: TO BE RECRUITED
3.	ANTICIPATED STARTING DATE	: JUNE 01, 1992
4.	STUDY DURATION:	: TWO YEARS FROM INITIATION
5.	TOTAL DIRECT COST:	: US$ 106,912.00
6.	SCIENTIFIC PROGRAMME HEAD	: This protocol has been approved by the Clinical Science Division.

Signature, Associate Director
Clinical Science Division

4/3/92
Date

7. ABSTRACT SUMMARY

The increasing prevalence of resistance to antimicrobial drugs of *Shigella* spp. in Bangladesh necessitates search for effective and safe alternative drugs. Cefixime is a broad spectrum, third generation, oral cephalosporin. It is resistant to the action of most common bacterial plasmid and chromosomally-mediated beta-lactamases, and has a long serum half-life that permit once daily administration. Cefixime has been evaluated for both efficacy and safety in children aged 6 months to 13 years having respiratory and urinary tract infections. Results indicate that cefixime is both effective in the treatment of such infections, and safe in children. Loose stools and skin rash are among the most common side-effects and discontinuation of drug is required in <2% of patients. Efficacy of cefixime has, however, not been evaluated in patients with acute dysentery due to *Shigella*. The minimum inhibitory concentrations of *Shigella* isolates have been determined to be in the range of 0.25-0.50 micrograms/ml. Serum concentrations of between 3-5 micrograms/ml of the drug are usually obtainable after a 400 mg oral dose. We have determined in vitro susceptibility of 239 clinical *Shigella* isolates to cefixime by Kirby-Bauer Method at the Clinical Research Centre. All isolates (100%) have been found to be susceptible.

This double-blind, randomized trial, will evaluate the effectiveness of a five-day course of cefixime as compared to pivamdinocillin (pivmecillinam was the previous name) in the treatment of shigellosis in adults, 18-60 years of age. Limited pharmacokinetic study to determine peak and trough serum concentrations, and stool concentrations will be done to define its optimal dose. A total of 70 patients with culture-confirmed *Shigella* dysentery who report to the Clinical Research Centre (CRC) with acute dysentery of $\leq$72 hours duration, and who have not been treated with effective antimicrobial drugs for their illness before attending the CRC, will be enrolled into the study after obtaining written informed consent. Patients with illnesses in addition to shigellosis, requiring antimicrobial therapy in addition to the study drugs, or patients with vegetative haematophagous *Entamoeba histolytica* in the stool sample will be excluded.

History will be obtained, and physical and laboratory examinations performed on admission and daily thereafter; findings will be recorded in pre-designed forms. After performing all admission procedures, patients will be randomly assigned to take either tablet pivamdinocillin in a dose of 400 mg every 6 hours, or tablet cefixime in a dose of 400 mg every 24 hours, for a total of 5 days. Therapy will be double-blind. Responses to therapy in the two treatment groups will be assessed by pre-defined bacteriologic and clinical cure rates. Incidences of adverse and toxic effects, their nature, severity, and impact on therapy will be systematically evaluated and recorded. Patients developing major side effects attributable to either of the drugs will be withdrawn from the study drugs and will be treated with effective alternative drug after opening the treatment codes. Patients who do not improve by day-3 of treatment will also be regarded as "Clinical Failures", and will be treated with an effective alternative drug without opening the drug codes.

SECTION II: RESEARCH PLAN

A. INTRODUCTION

A.1 Objectives

The objectives of the study are:

A.1.1 To compare effectiveness of cefixime with that of pivamdinocillin in the treatment of shigellosis.

A.1.2 To perform limited pharmacokinetic studies, i.e. to measure the peak and trough serum concentrations of both the drugs, and also to measure their concentrations in the stools.

A.2 Study Background

A.2.1 *Shigella* morbidity and mortality

Shigellosis remains a major cause of diarrhoea associated death in children in many developing countries including Bangladesh [1-3]. It is estimated that, of the approximately 3.8 million diarrhoea related deaths that occur worldwide in children annually (excluding China), 0.5 million are attributable to shigellosis [4]. In the Matlab field study area of the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B), approximately two-thirds of all diarrhoea related deaths are caused by dysentery [2]. Based upon the results of studies conducted in other areas of Bangladesh, it is likely that more than half of these children with dysentery are infected with *Shigella* [1].

A.2.2 Benefits of antimicrobial therapy of shigellosis

Treatment of patients with shigellosis with an effective antimicrobial agent is known to shorten both the duration of symptoms, as well as the duration of excretion of the organisms in the stool [5-7]. Early treatment with effective antimicrobials can prevent most deaths that occur due to shigellosis [5,8,9,10], especially in association with toxic colitis [11], haemolytic-uraemic syndrome [12], and sepsis [13].

A.2.3 The problem of multiply-resistant *Shigella*

Effective treatment of shigellosis has been complicated by the recent emergence of multi-resistant strains of *Shigella* [14-16] (Figures 1-3). These strains are resistant to ampicillin, trimethoprim-sulphamethoxazole, and nalidixic acid, which until recently had been the drugs of choice for treating shigellosis [7]. In 1990, 418/585 (71%) of *S. dysenteriae* type 1 isolates from patients presenting to the Clinical Research Centre of the ICDDR,B, were resistant to ampicillin and 410/585 (69%) were resistant to trimethoprim-sulfamethoxazole (Figure-2). Over 50% of *Shigella flexneri* isolates were resistant to ampicillin, and about 40% to trimethoprim-sulphamethoxazole. About 58%

of the *S. dysenteriae* type 1 isolates were resistant to nalidixic acid, which until recently had been the drug of choice for empiric treatment of patients with suspected shigellosis presenting to the Clinical Research Centre of ICDDR,B (Figure-2). Almost all resistant *S. flexneri*, however, remain susceptible to nalidixic acid.

For patients infected with strains of *Shigella* resistant to ampicillin, trimethoprim-sulphamethoxazole and nalidixic acid, there are currently few alternative treatment options. Few other antimicrobial agents that remain active in vitro, and that has been shown to be effective in controlled clinical trials are pivamdinocillin; a third generation cephalosporin, ceftriaxone; and newer quinolones [17,18,25,26]. Pivamdinocillin has been shown to be effective in the treatment of shigellosis in adults [17], and ceftriaxone in both adults and children in controlled clinical trials [25,26]. It is likely that, as with the other ß-lactam agents, resistance will eventually develop against these agents once it is widely used. Ciprofloxacin, a newer quinolone, is another potential drug for the treatment of shigellosis. In controlled clinical trial at the Clinical Research Centre of ICDDR,B, ciprofloxacin has been shown to be effective in the treatment of adults with shigellosis [18]. However, quinolones are known to cause arthropathy in animal models [19,20], and its safety for use in children has yet to be established. Thus, there is a pressing need to find additional effective antimicrobial therapies for shigellosis [21].

A.2.4 Previous trials of cephalosporins in shigellosis

There have been at least 3 previous studies of first and second generation cephalosporins in the treatment of shigellosis. In a randomized trial, both bacteriologic clearance of faeces and clinical improvement with cephalexin (a first generation oral cephalosporin) was inferior to that of ampicillin, although cephalexin was found to be effective against *Shigellae* as determined by in vitro tests [22]. Difference between in vitro and in vivo tests was ascribed by the author to be due to reduced inhibitory action of cephalexin in serum; serum bactericidal concentrations were determined to be double than that determined by in vitro tests [22]. Similarly, another first generation cephalosporin, cephaloglycin, was found to be ineffective in the treatment of shigellosis [23]. A second generation parenteral cephalosporin, cefamandole, was similarly evaluated in a randomized, non-blinded study to be ineffective in the treatment of shigellosis in children despite the low minimum inhibitory concentrations (MIC) and minimum bactericidal concentrations (MBC) of the drug, and a much higher serum concentration that can be attained [24]. The sample size was small, however, the activity was very much inferior to trimethoprim-sulphamethoxazole and ampicillin [24].

In contrast to these studies of first and second generation cephalosporins, two studies of the third generation parenteral cephalosporin, ceftriaxone, was found to be effective in the treatment of shigellosis in both adults and children [25,26]. The limitations for

use of ceftriaxone include the need for hospitalization and high cost of the drug.

A.2.5 Antibacterial activity of cefixime

Cefixime is an oral third generation cephalosporin [27], and has a broad spectrum of antimicrobial activity against both gram-positive and gram-negative bacteria, and is similar to that of the parenterally administered third generation cephalosporins [28-30]. It is less active than the first and second generation cephalosporins against gram-positive bacteria, but it is more active against gram-negative organisms [30]. Both beta-lactamase positive and negative *H. influenza, N. gonorrhoeae*, and *Branhamella catarrhalis* are inhibited at concentrations $\leq$0.06 microgram/ml of cefixime [29]. Minimum inhibitory concentrations for *Salmonella* and *Shigellae* has been determined to be 0.25 microgram/ml. Also, ampicillin, chloramphenicol, and trimethoprim-sulphamethozaxole resistant organisms have been shown to be inhibited by <1 microgram/ml of cefixime [28-30]. Cefixime is ineffective against *Pseudomonas* spp. and *Bacteroides fragilis* with MICs determined to be >32 micrograms/ml [28-31]. We have recently tested in vitro susceptibility of 239 clinical *Shigella* isolates (*S. dysenteriae* type-1: 77, *S. flexneri*: 112, *S. boydii*: 20, *S. sonnei*: 22, and *S. dysenteriae* type 2-10: 8) to cefixime, pivamdinocillin, nalidixic acid, ampicillin, trimethoprim-sulfamethoxazole, and ciprofloxacin (unpublished). All isolates were susceptible to cefixime, while 3/112 (2.7%) of *S. flexneri* and 2/20 (10%) of *S. boydii* were resistant to pivamdinocillin; 98% of all *Shigella* isolates were, thus, susceptible to pivamdinocillin. Cefixime is not inactivated by most of the common plasmid and chromosomal beta-lactamases and undergoes slight hydrolysis by the *E. cloacae* P99 chromosomal beta-lactamase at low concentrations of the substrate [29]. Unlike other oral cephalosporins, hydrolysis of cefixime by the oxacillin and carbenicillin hydrolyzing plasmid-mediated beta-lactamases is minimal [28,29]. In a study to identify the types and amounts of beta-lactamase produced by 35 strains of *S. flexneri*, and 41 strains of *S. dysenteriae* type 1 from rural and urban areas of Bangladesh, 54 strains were found to produce plasmid mediated beta-lactamase, 18 strains were found to produce chromosomally mediated cephalosporinase, and 2 strains were found to produce TEM-1 type beta-lactamase (Michael L. Bennish, Personal communication). Compared to other orally absorbable cephalosporins, cefixime has a 20-fold greater affinity for PBP-3 (penicillin-binding-protein) which is the major binding site for cephalosporins, and also has a high affinity for PBP 1b which explains the rapid lytic action of cefixime; this activity is even more than many of the parenteral cephalosporins [29].

Cefixime has not been evaluated for the treatment of shigellosis. Clinical trials in the treatment of respiratory tract infections and urinary tract infections indicate that cefixime is an useful agent for the treatment of such infections [32-35].

A.2.6 Pharmacokinetics of cefixime

Absorption of cefixime after an oral dose is low; about 40%-52% of the drug is absorbed after an oral dose, and absorption is not affected by a meal [27,37]. Absorption is slow, and peak serum concentrations are attained between 2-5 hours after an oral dose [31]. Serum free-fraction of cefixime has been determined to be about 30%, and although there is a linear increase in serum level with increasing dose, the increase is not directly proportional to dose [27]. Cefixime has a half-life of about 3-4 hours which is longer than oral first and second generation cephalosporins, and the half-life is dose independent [27,38,39]. Volunteer study indicate that after an oral dose of 400 mg, mean peak concentrations in the range of 3-5 microgram/ml is achieved in the serum, and corresponding value for a 200 mg dose is about 2-4 microgram/ml, obtained approximately 4 hours after the dose [27,38]. Cefixime is also excreted in bile [31]. Longer half-life allow less frequent, once or twice daily administration possible [40,41]. In normal individuals, accumulation of the drug is not seen to occur with multiple-doses administered for 2 weeks [27]. However, in patients with renal disease with decreasing creatinine clearance, protein binding of cefixime declines with increase in elimination half-life. Dose adjustment is required when creatinine clearance falls below <20 ml/min per 1.73m [42]. Between 18%-41% of the absorbed drug is excreted unchanged in the urine within 24 hours [27]. Unlike cephalexin, the activity of cefixime is not reduced in presence of serum, blood or urine [29]. Pharmacokinetic parameters in children are similar to those measured in the young and elderly adults [27].

A.2.7 Safety of cefixime

The incidence of adverse effects occurring in patients receiving cefixime for respiratory tract infections have been reported to vary between as low as 7% to as high as 60%. Adverse effects are usually mild in nature and diarrhoea and stool changes are the most common side effects of cefixime. Discontinuation of drug for adverse effects are required in about 1% of patients [32-35]. Review of the safety studies of cefixime in 1575 adults (both men and women), and 615 children with respiratory and urinary tract infections, who had received cefixime in either single daily dose, or 12-hourly doses indicate that it is a safe drug for the treatment of these infections [41]. Adverse experiences that have been observed in >2% of adults and children receiving cefixime include diarrhoea (10.3%-15%), stool changes (8.5%-15.6%), headache (2.1%-15.8%), abdominal pain (2.7%-6.4%), skin rash (3.2%-6.7%), vomiting (3.2%-3.5%), dizziness (2.6%- 4.3%), dyspepsia (1.8%-4.3%), and pruritus (2.0%-2.8%). However, moderate to severe drug-related experience include diarrhoea (4.8%-8.1%), stool changes (0.7%-3.1%), headache (0% -2.4%), abdominal pain (0.7%-2.5%), vomiting (0.3%-0.7%), dizziness (0.2%-0.8%), dyspepsia (0.2%-1.3%), and pruritus (0.4%-1.0%) of patients receiving cefixime. Diarrhoea occurs early during a course and the incidence of *Clostridium* associated colitis is <0.1%. Drug-related liver function and blood abnormalities are even

rare; most common abnormalities include elevation of serum amylase (1.5%-4.6%), elevation of serum glutamine aminotransferase (0.2%-1.2%), elevation of serum alanine aminotransferase (0.7%-0.5%), eosinophilia (0.1%-1.3%), and thrombocytopenia (0.4%-0.9%) [41].

A.2.8 **Registration Status; Manufacturer; Country of Origin of Cefixime:** Cefixime is not a registered drug in Bangladesh. It has been marketted in the United States in the brand name of "Suprax" by the pharmaceutical company named "Lederle". The drug is registered for free sale in the United States, in many European countries, and in Japan for the last several years.

A.2.9 **Comparative Cost of Antimicrobial Therapy for Shigellosis**

Cefixime has not yet been marketted in Bangladesh. Therefore, only speculation is possible with regard to the cost of a course of cefixime for the treatment of shigellosis. Generally, newer antimicrobials are more expensive than the older ones. The current first-line drug nalidixic acid is the cheapest, and cost of therapy for an adult with this agent is about Tk 100.00 only. The cost for another drug, pivamdinicillin (Selexid is the brand name) is about Tk 400.00 only. The cost for ciprofloxacin is Tk 240.00 only, however, its safety for use in children has not been established. The only other drug that has proven efficacy in the treatment of shigellosis and is available in Bangladesh is ceftriaxone. The cost of therapy of adults with this agent will be at least Tk 6,600 only. The cost for a 5-day-course of cefixime for the treatment of adults in the United States is about US$ 22.00, i.e. about Tk 850.00 only. Usually, the cost of drugs in Bangladesh is at least half of that in the United States, or Europe. Therefore, the cost of a course of therapy with cefixime in Bangladesh is expected to be around Tk 400.00 only which is very similar to that of pivamdinocillin, one of the two currently used drugs for the treatment of shigellosis.

B. METHODS OF PROCEDURE

The design of this study will be similar to the three previous clinical studies of the treatment of shigellosis that we have conducted at the Clinical Research Centre of ICDDR,B.

B.1 **Sample Size Determination**

Results of a recently completed study in the Clinical Research Centre of ICDDR,B (Dr. R. Islam; Personal communication) shows that pivamdinocillin (pivmecillinam) therapy was successful in 100% of children treated for acute dysentery due to *Shigella*, as assessed on day five of the study. We consider, to be useful as an alternative drug for the treatment of shigellosis, clinical success should occur in at least 80% of cefixime treated patients. To show this difference in clinical success, we estimate a sample size of 32 patients (let us say 35) in each group, with type-I error of 0.05, and type-II error of 0.2. The following formula was used in calculating sample size;

$$n = \frac{P_1\,(100-P_1) \pm P_2\,(100-P_2)}{(P_1 - P_2)^2} \times f\,(\ ,\ )$$

B.2 **Selection criteria**

B.2.1 Age: 18-60 years

B.2.2 Sex: Either sex

B.2.3 Duration of diarrhoea before coming to hospital: $\leq$72 hours

B.2.4 Stool characteristics: Frank bloody, or bloody-mucoid on inspection

B.3 **Exclusion criteria**

B.3.1 Patients who do not give written consent to participate in the study.

B.3.2 Prior therapy with an antimicrobial effective against *Shigella*

B.3.3 Demonstration of erythro-phagocytic trophozoites of *Entamoeba histolytica* on stool microscopic examination.

B.3.4 Presence of any other infectious illness that will require treatment with antimicrobial in addition to the drugs under study. Other concomitant infections will include pneumonia, meningitis, suspected septicaemia etc.

B.3.5 Patients with known history of allergy to beta-lactam antibiotics.

B.3.6 Patients who are initially enrolled into the study, but subsequently both of their admission stool and rectal swab cultures fail to grow *Shigella*.

B.4 **Requirement of informed consent**

Written informed consent will be required from the patients.

B.5 **Screening of the patients for study**

Will began after 0700 hours in the morning and continue until 1330 hours only in order to permit history taking, physical examination, stool microscopic examination, and first sampling of blood for serum concentration of the drugs within 17:30 hours.

B.6 **Place for conduction of the study**

Patients will be admitted into the Clinical Study Ward of the Clinical Research Centre (CRC).

B.7 **Clinical Evaluation and Laboratory Studies**

Patients will be hospitalized for full six days after the initiation of therapy, and will be requested to return 7 days after discharge. The followings will be the schedule for the routine clinical and laboratory evaluations (please see flow chart: Annexure-A).

B.7.1 History and physical examination: On admission and daily thereafter during the whole study period, and at follow-up 7 days after discharge.

B.7.2 Determination of vital signs: Such as pulse/heart rate, oral temperature, respiratory rate, blood pressures every 4 hourly throughout the study period.

B.7.3 Enumeration and characterization of stools: Daily, throughout the study period. Patients will be required to collect individual stool irrespective of volume onto a plastic lined, non-absorbable diapers (as used in three previous studies). This will enable characterization of individual stools, and also, determination of stool frequency by counting the number of diapers.

B.7.4 Stool culture for identification of *Shigella* and *Salmonella*: Will be done on admission before starting study drugs and on study day-3.

B.7.5 Rectal swab cultures for identification of *Shigella*: Will be performed on the admission day prior to start of study drugs, on all subsequent days of hospitalization, and at follow-up visit 7 days after discharge.

B.7.6 In vitro susceptibility of the *Shigella* isolates to cefixime, ampicillin, trimethoprim-sulfamethoxazole, nalidixic acid, pivamdinocillin, and ciprofloxacin will be tested by Kirby-Bauer method [36].

B.7.7 Determination of minimum inhibitory concentrations (MIC) of the study drugs to all *Shigella* isolates will be performed by broth dilution technique.

B.7.8 Determination of MIC of the study drugs in serum against corresponding *Shigella* isolates of the patients will be performed.

B.7.9 Complete blood count, platelet count, serum electrolytes (Na^+, Cl^-, K^+, HCO_3), serum total protein, and serum creatinine (total 5 ml of blood) will be done on admission before initiation of study drugs. They may also be performed on any other day, only if considered necessary for the management of the patient.

B.7.10 Peak serum concentrations of the study drugs (1 ml of venous blood on each occasions): 90 minutes, and 4 hours after the first dose of medication on the first study day.

B.7.11 Trough serum concentrations of the study drugs (1 ml of venous blood): To be determined on venous blood sample drawn 1 minute before the 5th dose of study drugs (first dose of study day-2).

B.7.12 Stool concentrations of the study drugs: To be determined from an aliquot of first stool (about 5 gram) of the study day collected on study days 2 and 6.

B.7.13 Urinalysis: Will be performed only if indicated for the management of the patient.

B.7.14 Radiological studies: Will be done only when indicated for management of the patients.

B.7.15 Laboratory Methods

All cultures and haematologic and biochemical examinations will be done using routine methods now available in our laboratories. Determination of serum and stool drug concentrations will be done using a chromatographic method. For this study, a total of between 13-14.5 ml of blood will be required for the tests listed in the methods section.

B.8 **Treatment Regimens**

Patients will be randomized in equal numbers to receive either 400 mg of cefixime once every 24 hours, or 400 mg of pivamdinocillin every 6 hours starting from the beginning of the study, for a total of five days. In order to make the therapies double-blinded, the cefixime treated group will receive active drug for the first dose of the day

followed by placebo for pivamdinocillin for the next 3 doses, on 5 consecutive days. Pivamdinocillin treated group will receive 400 mg of active drug every 6 hourly.

B.9 **Concomitant Therapy**

No other antimicrobial will be used other than the study drugs. Patients who require such therapy from the beginning of the study will not be enrolled. If any patients require such therapy after enrollment in the study, the will be withdrawn from the study without opening their drug codes, and they will be treated with appropriate drugs. Only some patients with oral temperature of $\geq 39^{o}C$ will receive paracetamol (acetaminophen) as concomitant therapy. It is hoped that the randomization procedure will help distributing such cases equally in the two study groups. However, such cases will be taken into account during efficacy evaluation and analysis.

B.10 **Diets**

The adult patients of this study will receive usual adult diet of the CRC.

B.11 **Rehydration**

Severe dehydration among adult patients with shigellosis is extremely rare. Consequently, almost every patients with dehydration will require only rice ORS (standard rehydration fluid used in the CRC) for the correction of their dehydration, and for maintenance of hydration. However, if oral rehydration is not possible, intravenous fluids will be used for rehydration. Dehydration status on admission, proportion of patients rehydrated with oral and intravenous rehydrations, and the amount of such fluids required will be taken into account during analysis.

B.12 **Randomization**

Patients will be assigned a study number upon enrollment into the study. Such study numbers will be assigned consecutively, and a study medication will have been randomly pre-assigned to each study number. Randomization will be done using a block randomization method with a fixed block size of four.

B.13 **Evaluation of Outcome**

B.13.1 Primary response variables are;

a. Bacteriologic cure

b. Clinical cure

c. Withdrawal from study due to therapeutic failures

d. Bacteriologic relapse

e. Withdrawal of study drug because of adverse/toxic effects.

B.13.2 Secondary response variables are;

a. Incidences, nature, and severity of adverse effects.

b. Daily, and total stool frequency.

c. Stool characteristics: Time to first watery, soft and formed stools, last bloody-mucoid, watery, and soft stools.

d. Presence of blood and mucus in stools: Time to last blood, and last mucus in stools.

e. Fever: Time to last fever (>37.8^{o}C).

f. Straining/tenesmus: Presence of straining/tenesmus on every study day, and time to last straining/tenesmus.

g. Abdominal pain and tenderness: Presence of pain/tenderness, and time to last abdominal pain and tenderness.

h. Number of WBCs and RBCs in stool on microscopic examination on study day-3 and on study day-5.

i. Number of cases with negative culture for *Shigella* on each study days.

C. **Definitions**

C.1 **Bacteriologic cure:** Bacteriologic cure will be said to have occurred if *Shigella* can not be isolated from stool/rectal swab samples on study day-3 and on any subsequent study days.

C.2 **Bacteriologic relapse:** If stool/rectal swab culture after becoming negative for *Shigella* on two consecutive days become positive again.

C.3 **Reinfection:** Will be defined as infection due to a different strain of *Shigella*, or same strain with a different antimicrobial susceptibility pattern than the original strain identified at the beginning of the study.

C.4 **Clinical cure:** This will be judged on the basis of patient's status on study day 5. Patients having either, "Resolution of illness", or "Marked improvement", will be considered to have "Clinical Cure", and those having "Slight improvement", or "Failure" will be considered to have "Clinical Failure". Grading the responses into the above mentioned categories will be done as follows.

C.4.1 Resolution of illness:
- No frank dysenteric stool on naked eye examination.
- No watery stool
- $\leq$ 3 total stools within 24 hours.
- Afebrile.

C.4.2 Marked improvement:
- No frank dysenteric stool on naked eye examination.
- $\leq$ 1 watery stool.
- $\leq$ 6 total stools.
- Afebrile.

C.4.3 Slight improvement:
- Upto 1 dysenteric stool on naked eye examination.
- $\leq$ 3 watery stools
- $\leq$ 9 total stools.
- Afebrile

C.4.4 Failure: >1 dysenteric stools on naked eye examination, or

> 3 watery stools, or

> 9 total stools, or

Febrile.

C.4.5 **Clinical failure determined on study day-3**: Response to therapy will also be determined at the end of study day-3. This is the time when antimicrobial susceptibility results of pathogens are usually available. If no improvement of patients condition is observed, i.e., if the patients remain febrile; continue to have same stool characteristics as on admission; continue to have frank blood in stools; stool frequency is either not decreased, or increased; patients continue to have moderate or severe abdominal pain, and/or tenderness on light palpation; patients found to be toxic etc., will be considered to have "Clinical Failure" and they will be analyzed together with the "Clinical Failures" as described under C.4.4.

C.5 **Fever**: Oral temperature of >37.8^{o}C

C.6 **Frank dysenteric stool**: Stool that contains only mucus and blood; no faecal matter.

C.7 **Watery stool**: That can be poured easily from one container to another like water, either without, or with insignificant adherence to the surface of the container.

C.8 **Soft stool**: That can not be poured like water from one container to another, or can be poured with difficulty with considerable adherence to the surface of the container. However, when placed in a container soft stool takes the shape of the container fairly rapidly.

C.9 **Formed stool**: That retains its shape.

C.10 **Withdrawal from study:**

C.10.1 **For Failure to Respond**

This will be determined at the end of study day-3, as described under C.4.5. Such patients will have their study drugs discontinued without opening drug codes, and they will be treated with effective alternate drug as determined by in vitro susceptibility of the infecting *Shigella*. Such cases will not be replaced by fresh cases.

C.10.2 **For major side effects**

This will include anaphylaxis or anaphylactoid reaction, severe diarrhoea etc. that can be attributed to either of the study drugs. Such cases will have their drug codes opened, and they will be treated with an effective alternative drug as determined by in vitro susceptibility of the infecting *Shigella*. These cases too, will not be replaced by fresh cases.

C.11 **Handling of Treatment Failures**

If the study treatment is judged to have failed by either clinical or bacteriologic criteria, study drugs will be discontinued without opening drug codes, and such patients will be treated with an effective alternative drug (if available). In addition to the evaluation to be performed on study day-5, therapy will be considered to have failed if after 72 hours of therapy patients have not shown symptomatic improvement and continue to have visible blood and mucus in stools, fever and tenesmus.

The development at any time during the study of an adverse reactions (skin rash, joint pain, swelling, anaphylaxis, anaphylactoid reactions etc.) that is possibly or probably related to drug therapy will be an indication for stopping of the study drug, opening drug codes, and starting alternative therapy. As mentioned earlier, failure rates in two groups will be compared during analysis.

C.12 **Statistical Methods**

Difference in means will be tested for significance using the Student's t test if the data is normally distributed, and the Mann-Whitney U test if the data is non-normally distributed. Differences in proportions will be tested for significance using the Chi-square test. Statpac Gold version 3.2 will be used for data entry into the computer, and both Statpac Gold and SPSS-PC$^+$ will be used for data analysis.

D. **SIGNIFICANCE**

This study is intended to identify another antimicrobial agent that is likely to be effective in the treatment of shigellosis. There is currently a crucial need for identifying such agents as the majority of *S. dysenteriae* type 1 isolates which are responsible for the most severe forms of shigellosis are resistant to all commonly used drugs except pivamdinocillin. Although ciprofloxacin has been shown to be effective in adults with acute dysentery due to *Shigella*, its safety for use in children is yet to be determined. Under the present circumstances, it is likely that soon pivamdinocillin will replace

nalidixic acid as empiric first-line drug for the treatment of shigellosis, and this is the reason for selecting pivamdinocillin as the control drug for this proposed study.

E. Facilities Required

This study will be done using the current facilities of the Clinical Research Center.

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ABSTRACT SUMMARY

1. **Requirements for Study Population**

This study will require adults aged between 18 years to 60 years who are ill with dysentery caused by infection with *Shigella*. Because of the problem of emergence of resistance against antimicrobials it is essential to identify effective antimicrobial therapies for shigellosis. Cefixime has been shown to be effective against *Shigella* as determined by in vitro tests, and is a safe drug. It is now necessary to determine its effectiveness in the treatment of shigellosis before any recommendation can be made.

2. **Potential Risks**

The major potential risk from the study drugs are the adverse reactions. Both pivamdinocillin and cefixime are known to be quite safe. The major adverse reactions to pivamdinocillin are similar to those seen with other ß-lactam agents. The most serious of these are allergic reactions, and rarely anaphylaxis. Other reported adverse reactions to pivamdinocillin include nausea, dyspepsia and other gastrointestinal complaints in <5% of patients who receive the drug, and slight elevation of liver enzymes. Adverse effects of cefixime include gastrointestinal disturbances such as nausea, anorexia, diarrhoea, vomiting, abdominal pain etc. Hypersensitivity reactions such as skin rash, pruritus, urticaria, anaphylactoid reactions, and mild elevation of aminotransferases can occur. Most of the adverse reactions are of mild to moderate severity and discontinuation of drug is needed only in <2% of cases. Aside from adverse effects of the drugs, the only other risk associated with this study is the blood drawing. The volume of blood drawn for study purposes will be quite small, and pose no risk to the study patients.

3. **Methods for minimizing potential risks**

Patients will have a detailed physical examination performed daily. Any patient complaining any symptom on any study days and during the follow-up visit that may have some relation with administration of the study drugs will be recorded. If any such adverse effect is considered to be of such nature or severity that continuation of drug may cause physical injury to the patients, study drug will be discontinued, drug codes will be opened, and such patients will be treated with appropriate effective drug.

4. **Methods for safeguarding confidentiality**

Patients will be assigned a study number and all data entry and computer records will be identified using this study number rather than the patients' name. No one other than the investigators of the study will have any access to the records.

5. **Informed consent**

Informed consent will be obtained from the patients enrolled in the study. Bangla and English language versions of the informed consent form are attached.

6. Interview

Patients will have routine medical interviews and examinations done on a daily basis.

7. **Benefits to the individual and society**

The individual will benefit because they will receive treatment for shigellosis with one of two drugs that are likely to be effective in its therapy. Given the widespread resistance of *Shigella* to other antimicrobial agents and the seriousness of the morbidity (and mortality) that is associated with *Shigella* infections that are not treated or are treated ineffectively, the benefits of therapy with these two drugs far outweigh the risks. Society will benefit because we will determine the effectiveness and safety of these two drugs, pivamdinocillin and cefixime, in the treatment of shigellosis. This will allow us to plan more rational therapy for patients with this disease which is a major cause of childhood mortality and morbidity in Bangladesh and other developing countries.

8. **Samples required**

This study will make use of patient records, as well as stool, urine and blood.

SECTION IV: STUDY BUDGET

1.	**Personnel**		US$	29,000
1.1	**Charge-in**			
	Dr. M. A. Salam	25% x 24 m	: US$	7,000
	Dr. Wasif Ali Khan	25% x 24 m	:	4,500
	Mr. Humayun Kabir	25% x 24 m	:	2,500
	Mr. Rafiqul Islam	20% x 24 m	:	3,000
	Total		:	17,000
1.2	**New Recruitment**			
	Trainee Physician	100% x 2 x 24 m	:	8,000
	Trainee Lab Research Officer	100% x 1 x 24 m	:	4,000
	Total			12,000
2.	**Patient hospitalization**			**16,950**
2.1	70 study patients x 7.0 days x US$ 30/d		:	14,700
2.2	25 study patients x 3 days x US$ 30/d		:	2,250
3.	**Clinical pathology investigations**			**1,775**
3.1	Stool microscopy			
	70 study patients x 4 tests/pt x US$ 1.65/test		:	462
	25 culture negative patients x 1 test/pt x US$ 1.65		:	42
3.2	Urine analysis			
	25 study patients x 1 tests/pt x US$ 4.0/test		:	100
	10 culture negative patients x 1 test/pt x US$ 4.0/test		:	40

3.3	Peripheral blood T/C, D/C, Hct%	
	70 patients x 2 tests/patient x US$ 3.85/test :	539
	25 culture negative patients x 1 test/pt x US$ 3.85 :	97
3.4	Peripheral blood Platelet count, RBC morphology	
	70 patients x 2 test/patient x US$ 3.0/test :	420
	25 culture negative patients x 1 test/pt x US$ 3.0/test :	75
Total		1,775
4.	**Biochemistry investigations**	**2,314**
4.1	Serum electrolytes, protein, and creatinine	
	70 study patients x 2 tests/patient x US$ 9.02/test :	1,263
	25 culture negative patients x 1 test/pt x US$ 9.02 :	226
	Total	2,314
5.	**Microbiological tests**	**8,773**
5.1	Rectal swab culture for Shigella, and Salmonella	
	70 study patients x 7 tests/patient x US$ 6.00/test :	2,940
	25 culture negative patients x 2 tests/pt x US$ 6.00 :	300
5.2	Stool culture for *Shigella*, and *Salmonella*	
	70 study patients x 3 tests/patient x US$ 6.00/test :	1,260
	25 culture negative patients x 1 test/pt x US$ 6.00 :	150
5.3	Antibiotic susceptibility by Kirby-Bauer	
	70 patients x 2 tests/patient x US$ 4.58/test :	642
5.4	Stock culture & retrieval	
	70 patient x 2 stocks/patient x US$ 2.18/stock :	306

5.5	Determination of MIC (broth dilution)		
	70 isolates x 2 antibiotic x US$ 10.00/antibiotic	:	1,400
5.6	Determination of MIC in serum		
	70 isolates x 2 antibiotic x US$ 10.00/antibiotic	:	1,400
5.7	Blood culture & sensitivity		
	25 total patients x 1 test/patient x US$ 15/test	:	375
	Total		8,773
6.	**Pharmacokinetics**		**3,500**
6.1	Serum levels of antibiotics		
	70 study patients x 3 sample/patient x US$ 10.00	:	2,100
6.2	Stool levels of antibiotics		
	70 study patients x 2 tests/patient X US$ 10.00	:	1,400
7.	Follow-up transport cost reimbursement x 70 patient	:	400
8.	Office supplies	:	1,000
9.	Hospital supplies	:	500
10.	Laboratory supplies	:	500
11.	Non-stock supplies	:	1,500
12.	Xerox/mimeograph	:	200
13.	Medical illustration	:	250
14.	Local travel	:	500
15.	Transportation	:	1,000
16.	Rent/Comm/Utility	:	1,500
17.	Staff clinic subsidy	:	1,000
18.	Reprint	:	500
19.	Maintenance	:	250

20. Bioengineering	:	200
21. Travel	:	5,000

Net Operating Cost : US$ 76,612

Capital expenditure: US$ 5,000

Total direct cost : US$ 81,612

Overhead cost (31%): US$ 25,300

TOTAL PROJECT COST: US$ 106,912

SECTION V: CONSENT FORM

You are suffering from bacillary dysentery, which require treatment with an effective drug. Unfortunately, drugs may become ineffective after some years of use, necessitating search for effective alternatives. Cefixime is a new drug which, we think, is likely to be effective in the treatment of bacillary disease. We are conducting a study, and your participation in this study will enable us to determine if this new drug is effective in the treatment of the disease you are suffering from. If you participate in the study;

1. You will be required to stay in the hospital for 6 full days, and return 7 days after discharge for about an hour.

2. We will take detailed history, and perform thorough physical examination at admission and on every day; take small amount of stool on admission and two other days, and stool specimen from your rectum on admission and every day; draw blood (total of 14.5 ml, i.e. about 3 teaspoon) from your vein for different investigations two times on the admission day, and once on each of the two subsequent days for different investigations. All findings and results will be recorded.

3. You will receive either pivamdinocillin 400mg every 6 hours, or cefixime 400mg every 24 hours, for a total of five days. The former drug is being currently used for the treatment of bacillary dysentery at our centre. We will closely observe your progress and any side effect of the drugs that might occur. In case of serious side effects, study drug will be stopped, and you will be treated with an effective alternative drug.

4. You are the one to decide on your participation in the study. You will receive standard care of this centre, even if you do not participate in the study, and you may withdraw your consent any time during the study; your further treatment will not be affected by doing so.

5. All information obtained from you, including results of the laboratory investigations, will be kept confidential; no one other than the investigators will have access to those information. If you want to know the results of any or all the tests performed, we will provide you with the results, subject to availability.

If you are willing to participate please put your signature/LTI below.

Thank you for your cooperation.

Investigator's signature	Signature of witness	Signature of the patient
Date	Date	Date

আন্তর্জাতিক উদরাময় গবেষনা কেন্দ্র, বাংলাদেশ

সেফিক্সিম গবেষনা প্রকল্প
সম্মতি পত্র ॥

সুধী;

আপনি রক্ত আমাশয়ে ভুগছেন, যে রোগের চিকিৎসায় কার্যকর ঔষধের প্রয়োজন। দুর্ভাগ্যজনক এই যে, এ ধরনের ঔষধ কয়েক বছর ব্যবহারের পর অকেজো হয়ে পড়তে পারে। এ কারনে নতুন, কার্যকর ঔষধ খুঁজতে হয়। 'সেফিক্সিম' এমনি একটা নতুন ঔষধ, যা, আমরা মনেকরি, রক্ত আমাশয়ের চিকিৎসায় কার্যকর হতে পারে। আমরা এ গবেষনা কার্যক্রম হাতে নিয়েছি, যাতে আপনি অংশগ্রহন করে, এ ঔষধের কার্যকারীতা নির্নয়ে আমাদেরকে সহায়তা করতে পারেন। গবেষনায় অংশনিলে;

① আপনাকে পূর্ন ৫ দিন হাসপাতালে ভর্তি থাকতে হবে, এবং ছুটির ৭ দিন পর, প্রায় এক ঘন্টার জন্যে হাসপাতালে আসতে হবে।

② আমরা, ভর্তিরসময় এবং প্রতিদিন আপনার অসুখের বিস্তারিত বিবরন নেবো, এবং শারীরীক পরীক্ষা করবো; ভর্তির দিন এবং অন্য দু'দিন সামান্য পরিমানে মল, ভর্তির দিন ও পরবর্তী প্রতিদিন 'মলাশয়' থেকে সামান্য পরিমানে মলের নমুনা; ভর্তির দিন দু'বারে এবং তার পরবর্তী দু'দিন একবারে করে, চারবারে, সর্বমোট ১৪·৫ মি: লি, অর্থাৎ প্রায় ৩ চা'চামচ রক্ত বিভিন্ন পরীক্ষার জন্যে নিতে হবে। এসবের কারনে সাময়িক অস্বস্তি ও সূঁচের সামান্য ব্যথা ছাড়া আর কোন ক্ষতির সম্ভাবনা নেই।

③ ভর্তির পর, আপনাকে প্রতি ৬ ঘন্টা পরপর 800 মি:গ্রা: 'সিপ্রোফ্লোক্সাসিন' অথবা প্রতি ২৪ ঘন্টায় ১ বার 800 মি:গ্রা: 'সেফিক্সিম' সেবন করানো হবে। প্রথম ঔষধটি বর্তমানে এ হাসপাতালে, রক্ত আমাশয়ের চিকিৎসায় ব্যবহৃত হচ্ছে। আমরা আপনার প্রতি এবং ঔষধের কোন পার্শ্ব-প্রতিক্রিয়া হচ্ছে কি-না তা ঘনিষ্ট নজরে রাখবো। যেকোন পার্শ্ব-প্রতিক্রিয়া হলে তৎক্ষনাৎ গবেষনার ঔষধ বন্ধ করে অন্য কার্যকর ঔষধ দিয়ে আপনার চিকিৎসা করা হবে।

④ শুধুমাত্র আপনিই এ গবেষনায় আপনার অংশগ্রহনের ব্যাপারে সিদ্ধান্ত নিতে পারেন। আপনি এ গবেষনায় অংশগ্রহন না করলেও এ হাসপাতালের প্রচলিত সুচিকিৎসা পাবেন। যে কোন সময়, আপনি আপনার সম্মতি প্রত্যাহার করতে পারবেন, এবং এরফলে আপনি পরবর্তী চিকিৎসা থেকে বঞ্চিত হবেন না।

⑤ আপনার থেকে প্রাপ্ত সকল তথ্য গোপন রাখা হবে, এবং শুধুমাত্র গবেষকগন ছাড়া অন্য কেউই এসব তথ্য জানতে পারবেন না। আপনি ইচ্ছা করলে, ফলাফল জানা সাপেক্ষে, যে কোন বা সকল পরীক্ষার ফলাফল আপনাকে জানানো হবে।

আপনি এ গবেষনায় অংশগ্রহনে রাজী থাকলে, দয়া করে নীচের নির্দিষ্ট জায়গায় আপনার স্বাক্ষর বা টিপসই দিন।

আপনার সহযোগীতার জন্যে অসংখ্য ধন্যবাদ ॥

গবেষকের স্বাক্ষর

তারিখ

রুগীর স্বাক্ষর/টিপসই

তারিখ

সাক্ষীর স্বাক্ষর

তারিখ

ANNEXURE-A

Study Flow Chart of Cefixime in Shigellosis

Activity	Pre-Rx	During RX						Post-Rx
		D1	D2	D3	D4	D5	D6	D13
History	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X
Every 4h vital signs	X	X	X	X	X	X	X	
Stool culture for Shigella & Salmonella	X			X				
Rectal swab culture for Shigella	X	X	X	X	X	X	X	X
Stool enumeration & characterization		X	X	X	X	X	X	
Complete blood count	X							
Serum electrolytes (Na,K,Cl,$_2$2)	X							
Study drugs		X	X	X	X	X		
Serum concentrations of drugs		X	X					
Stool concentrations of drugs			X				X	

Figure 1

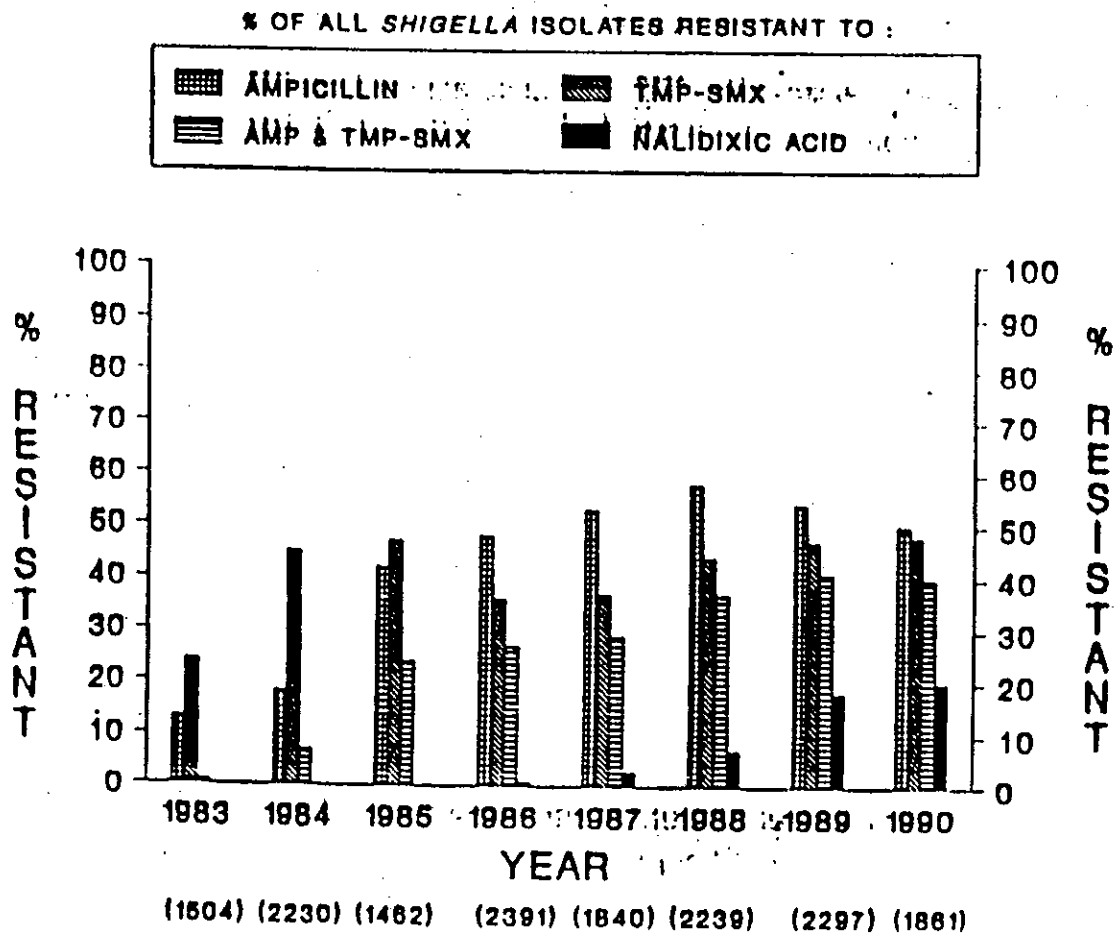

% OF ALL SHIGELLA ISOLATES RESISTANT TO :
AMPICILLIN
TMP-SMX
AMP & TMP-SMX
NALIDIXIC ACID
% RESISTANT
100
90
80
70
60
50
40
30
20
10
0
1983
1984
1985
1986
1987
1988
1989
1990
YEAR
(1604) (2230) (1462) (2391) (1840) (2239) (2297) (1861)

Figure 2

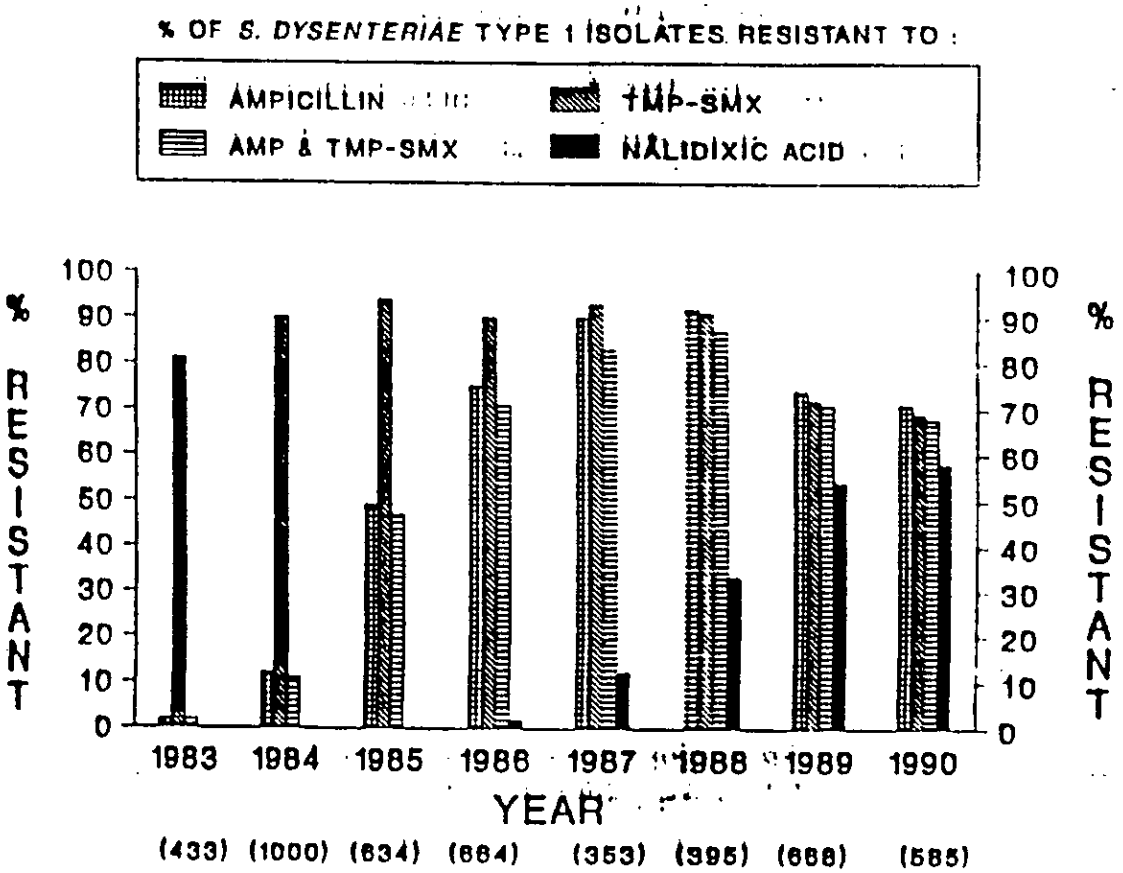
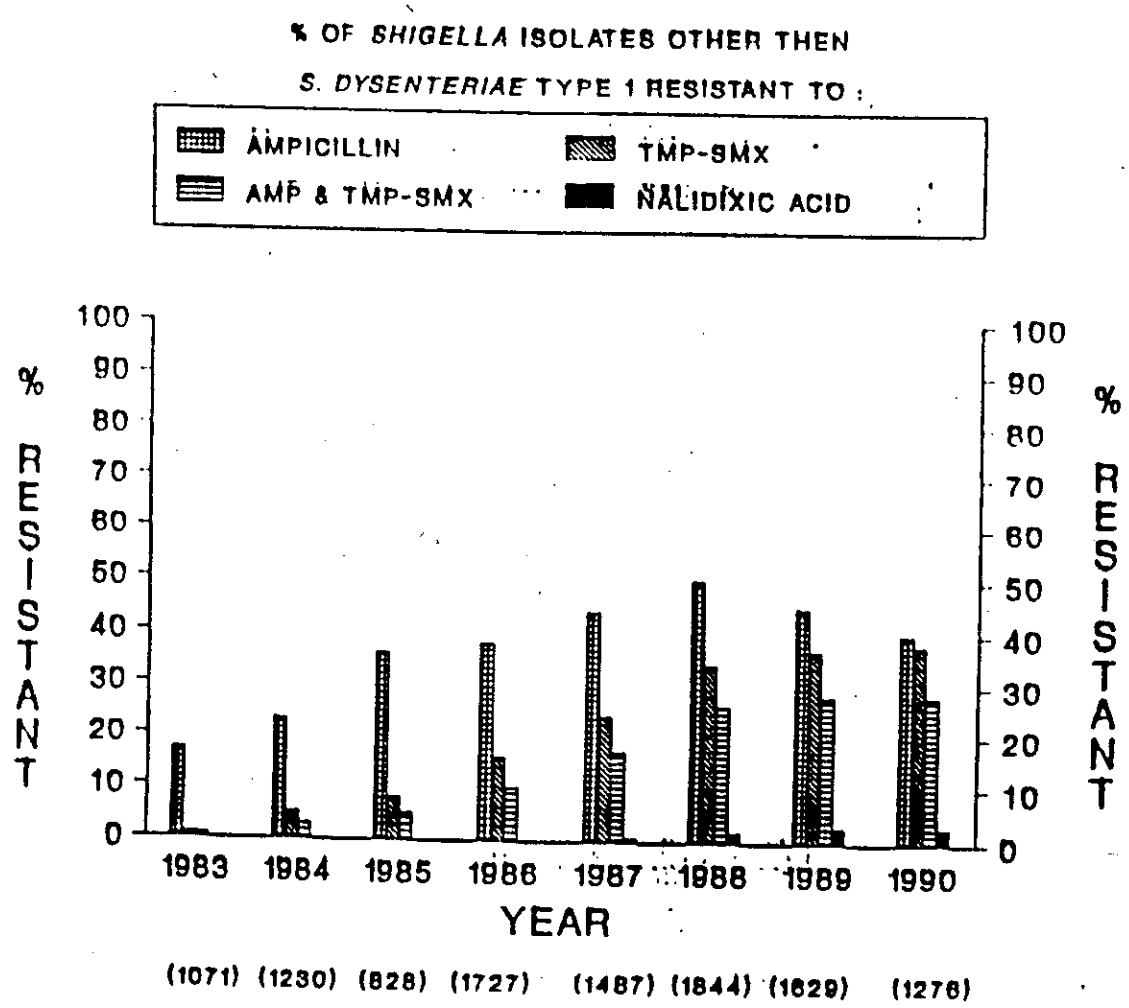

% OF S. DYSENTERIAE TYPE 1 ISOLATES RESISTANT TO :
AMPICILLIN
TMP-SMX
AMP & TMP-SMX
NALIDIXIC ACID
% RESISTANT
100
90
80
70
60
50
40
30
20
10
0
1983
1984
1985
1986
1987
1988
1989
1990
YEAR
(433)
(1000)
(634)
(664)
(353)
(395)
(668)
(585)

Figure 3


% OF SHIGELLA ISOLATES OTHER THEN
S. DYSENTERIAE TYPE 1 RESISTANT TO :
AMPICILLIN
TMP-SMX
AMP & TMP-SMX
NALIDIXIC ACID
% RESISTANT
100
90
80
70
60
50
40
30
20
10
0
1983
1984
1985
1986
1987
1988
1989
1990
YEAR
(1071)
(1230)
(828)
(1727)
(1487)
(1844)
(1629)
(1276)