Shigella dysenteriae type 1 with reduced susceptibility to fluoroquinolones

Sir—Epidemic dysentery caused by multidrug-resistant *Shigella dysenteriae* type 1 has been a recurrent challenge in many parts of the developing world. This organism caused an extensive epidemic of shigellosis in eastern India in 1984.[1] The strains isolated were resistant to streptomycin, tetracycline, and chloramphenicol; moderately sensitive to ampicillin, kanamycin, neomycin, and co-trimoxazole; and sensitive to nalidixic acid, furazolidone, and gentamicin. During this epidemic, highly encouraging results of treatment with nalidixic acid were reported.[2] However, within a short period, widespread use of this drug resulted in the emergence of nalidixic-acid-resistant *S dysenteriae* type 1 strains.[3]

After a lapse of about 18 years, an outbreak of bacillary dysentery was reported in April, 2002, among the labourers of tea gardens in eastern India. Investigations revealed an overall attack rate of 25·6%, with 16 deaths. Cases started increasing suddenly in affected tea gardens from the first week of April, 2002, and continued until the day of investigation in the second week of May, 2002. Children younger than 5 years were affected most, with an attack rate of 32·5%. The case-fatality ratio due to bacillary dysentery was 0·9%, and the death rate due to shigellosis among those admitted to hospital was 6%. The prominent clinical features of fatal cases were anuria, haematuria, dyspnoea, convulsions, and encephalopathy.

We examined stool specimens, with or without blood or mucus, from 30 patients using standard microbiological techniques.[4] Ten samples yielded an *S dysenteriae* type 1 strain. These ten patients presented clinically with fever, abdominal pain, tenesmus, and vomiting as well as bloody or mucoid stools. None had features of dehydration.

All ten *S dysenteriae* type 1 strains were resistant to ampicillin, co-trimoxazole, nalidixic acid, and norfloxacin, with intermediate susceptibility to ciprofloxacin; all were sensitive to ofloxacin. This finding indicates that indiscriminate use of antimicrobial agents by the local community has probably led to the development of resistance to fluoroquinolone derivatives, which are the only drugs until recently that are effective orally in treating multidrug-resistant *S dysenteriae* type 1. Ofloxacin is relatively expensive, and its use for shigellosis in the affected tea gardens is not common. The rational use of effective drugs in the community requires improvement of logistical support and community compliance to avoid further resistance.

This drug-resistant Shiga bacillus is likely to spread further in the near future, and will pose tremendous challenges among clinicians treating shigellosis. There is an urgent need for alternative drugs to treat drug-resistant shigellosis.

*K Sarkar, S Ghosh, S K Niyogi, S K Bhattacharya

National Institute of Cholera and Enteric Diseases, P-33, CIT Road Scheme XM, Kolkata 700 010, India
(e-mail: kamal412496@yahoo.com)

1 Pal SC. Epidemic bacillary dysentery in West Bengal. *Lancet* 1984; **1**: 1462.
2 Bose R, Nashipuri JN, Sen PK, et al. Epidemic of dysentery in West Bengal: clinicians' enigma. *Lancet* 1984; **2**: 1160.
3 Sen D, Dutta P, Deb BC, Pal SC. Nalidixic acid resistant *Shigella dysenteriae* type 1 in eastern India. *Lancet* 1988; **2**: 911.
4 World Health Organization. Manual for the laboratory investigation of acute enteric infections. Geneva: WHO, 1987; publication number WHO/CDD/83.3 rev 1.

Need for a true placebo for vaginal microbicide efficacy trials

Sir—Researchers must pay close attention to the selection of comparison groups in vaginal microbicide trials, or the results will be difficult or impossible to interpret. A true placebo product should be clincally indistinguishable from the potential microbicide and should have no effect, positive or negative, on women's susceptibility to infection.

In Lut Van Damme and colleagues, study of the vaginal gel COL-1492 (Sept 28, p 971),[1] the rate of HIV-1 seroconversion was significantly higher among women using COL-1492 than those in the comparison group. Use of COL-1492 probably increased women's susceptibility to infection, as shown by the higher risk of infection among women who used the product more frequently. However, another contributing factor might have been that use of the comparison product, Replens, was protective. There is evidence to support this possibility, which was also noted by the study authors.

Both products contain carbopol and polycarbophil—negatively charged polymers that could have microbicidal properties. According to the manufacturer, "polycarbophil is a weak acid with a high buffering capacity. It maintains the vaginal pH in the physiological range, about 4·5, and thus helps protect against infection".[2] Replens was nearly as effective as COL-1492 in protecting mice from vaginal infection with herpes simplex virus type 2 infection,[3] and in a clinical trial, use of a polycarbophil gel had some activity against bacterial vaginosis[4]—a disorder that probably increases susceptibility to HIV-1 infection.

Each dose of COL-1492 contains 52·5 mg nonoxynol-9; Replens contains none. If that were the only difference between the two products, the trial might have been a fair assessment of nonoxynol-9. However, gram for gram, Replens has more than twice the acid-buffering capacity of COL-1492, and therefore contains substantially more carbopol or polycarbophil (personal communication, Thomas Moench, ReProtect). Negatively charged polymers are also the active ingredient in other potential microbicide products entering advanced clinical trials. The lower infection rate for women using Replens makes these other candidate products also seem more promising.

No established placebo product is known to have zero effect on women's susceptibility to HIV-1 infection. Accordingly, future microbicide efficacy studies will include, in addition to the active treatment group, a group of women who use a comparison gel that researchers hope will not affect susceptibility, and a comparison group who use no vaginal product.[5] All participants will be provided with male condoms. Inclusion of a "no-product" group is, however, not a panacea. That group cannot be made unaware of treatment assignment, and differences in risk behaviour and other biases are likely to be introduced as a result. Ideally, infection rates will be significantly lower in the group using the candidate microbicide than in the group of women using the placebo product and those using no product. If infection rates and risk behaviours are similar in the placebo and no-product groups, investigators might then have also identified a true vaginal placebo product.

*Peter H Kilmarx, Lynn Paxton

*BOTUSA Project, PO Box 90, Gaborone, Botswana (PHK); and National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA, USA (PHK, LP)
(e-mail: pbk4@cdc.gov)

1 Van Damme L, Ramjee G, Alary M, et al, for the COL-1492 Study Group. Effectiveness of COL-1492, a nonoxynol-9 vaginal gel, on HIV-1 transmission in female sex workers: a randomised controlled trial. *Lancet* 2002; **360**: 971–77.
2 Anon. Bioadhesion with polycarbophil: a new approach to progesterone delivery. http://www.columbialabs.com/learn/profcr8-vaggel.htm (accessed Nov 8, 2002).
3 Maguire RA, Bergman N, Phillips DM. Comparison of microbicides for efficacy in protecting mice against vaginal challenge with