*Prince of Wales Hospital, Hong Kong, Special Administrative Region (SAR); and †The Chinese University of Hong Kong, Hong Kong, SAR

References

1. World Health Organization. Severe acute respiratory syndrome (SARS). [cited 2003 Sep 26]. Available from: http://www.who.int/csr/sars
2. Department of Health, Government of Hong Kong Special Administrative Region. Severe acute respiratory syndrome. [cited 2004 Jan 19]. Available from: http://www.info.gov.hk/ info/sars/eindex.htm
3. Centers for Disease Control and Prevention. Updated interim U.S. case definition for severe acute respiratory syndrome (SARS). [cited 2003 Sep 26]. Available from: http://www.cdc.gov/ ncidod/sars/casedefinition.htm
4. Peiris JS, Chu CM, Cheng VC, Chan KS, Hung IF, Poon LL, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet. 2003;361:1767–72.
5. Yam WC, Chan KH, Poon LL, Guan Y, Yuen KY, Seto WH, et al. Evaluation of reverse transcription–PCR assays for rapid diagnosis of severe acute respiratory syndrome associated with a novel coronavirus. J Clin Microbiol. 2003;41:4521–4.
6. Rainer TH, Cameron PA, Smit D, Ong KL, Hung AN, Nin DC, et al. Evaluation of WHO criteria for identifying patients with severe acute respiratory syndrome out of hospital: prospective observational study. BMJ. 2003; 326:1354–8.
7. Chan PKS, Ng KC, Chan RCW, Lam RKY, Chow VCY, Hui M, et al. Laboratory diagnosis of SARS. Emerg Infect Dis 2004;10:825–31.
8. Lee N, Hui D, Wu A, Chan P, Cameron P, Joynt GM, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. N Engl J Med. 2003;348:1986–94.
9. Wong RS, Wu A, To KF, Lee N, Lam CW, Wong CK, et al. Haematological manifestations in patients with severe acute respiratory syndrome: retrospective analysis. BMJ. 2003;326:1358–62.
10. Yuen E, Chak WK, Rainer TH. Role of absolute lymphocyte count in the screening of patients with suspected SARS. Emergency Medicine. 2003;15:395–6.

Address for correspondence: Nelson Lee, The Chinese University of Hong Kong, Department of Medicine and Therapeutics, Prince of Wales Hospital, Shatin, Hong Kong; fax: 852-26375396; email: leelsn@yahoo.com

Malaria Control and Public Health

To the Editor: Malaria continues to cause disease and death in millions of persons living in areas of the world where it is endemic, despite 4 decades of research on vaccines, new drugs, and alternative methods of control. Still, by far the most effective method for reducing and controlling the impact of this disease is indoor residual spraying (IRS) of insecticides. The most cost-effective and safe insecticide has been, and in many instances still is, dichlorodiphenyltrichloroethane (DDT). This intervention is continually under scrutiny, and we address these issues in this letter.

Chen and Rogan (1) claim that DDT causes reduced duration of lactation and increased incidence of preterm births, and they posit that DDT used for malaria control would do as much harm as good. The validity of their arguments requires substantial evidence of a causal relationship between DDT and adverse consequences of DDT IRS for malaria control.

Chen and Rogan dismiss a field study on births and duration of lactation in South African mothers, some of whom occupied houses sprayed with DDT for malaria control (2). However, if claims of large numbers of adverse health effects of DDT IRS are correct, then the study should have detected large differences between DDT-exposed and unexposed populations. According to Chen and Rogan, the median duration of breastfeeding could be as low as 3–4 months when mothers are exposed to high levels of DDT. Thus, a cross-section of breastfeeding infants in the DDT-exposed population should, on average, have been considerably younger than in the unexposed population. In fact, the average age of breastfeeding infants was slightly greater in the DDT-exposed population (8.3 months versus 7.7 months). For both populations, only an insignificant fraction of mothers could not donate milk. Furthermore, twice the level of dichlordiphenylethylene (DDE, metabolic breakdown product of DDT) that is claimed to cause reduced duration of lactation in humans has no adverse affect on lactation in rats (3). The authors of the South African study (2) report no difference in rates of stillbirths between the sprayed and unsprayed areas.

The National Institute of Environmental Health Sciences study (4) reported a causal association between DDT and preterm and small-for-gestational-age births but this has not been replicated for African births. The study was not based on a random population of births, and no explanation is offered for including diverse categories of births in the study population.

An earlier study in Sri Lanka presented data on deaths attributed to malaria and to premature births years before DDT was used and years when DDT IRS was used in 21 districts (5). Districts varied greatly in levels of malaria endemicity. After DDT was introduced in 1946, levels of IRS in 21 districts were commensurate with levels of endemic malaria. After 1946, malaria deaths declined greatly and the reduction was greatest where DDT usage was highest. During the same period, deaths attributable to premature births increased slightly. Inves-tigators attributed this to "improvements in reporting and diagnosis rather than any declines in the health of expectant mothers, which on all other criteria showed improvement." (5). Spearman's correlation analysis for 21 districts shows that the increase in premature birth deaths was slightly greater in areas with less malaria and DDT use. Thus, the evidence does not support the idea that the reported increase in premature births was a side effect of DDT use. In any case, the increase in deaths attributable to premature births was orders

of magnitude less than the reduction in deaths directly caused by malaria and other conditions indirectly related to malaria (5).

Similar major benefits of DDT use were seen in Guyana, where in 2 to 3 years, near elimination of malaria halved maternal deaths and reduced infant deaths by 39% (6). Anemia-associated deaths in pregnant females were reduced from 10 to 2.3 per 1,000 adult deaths (7). There was no offset of infant deaths attributable to adverse effects of DDT. Data from Guyana are particularly relevant to the present issue because malaria control was entirely due to DDT, i.e., drug treatments were not included (7). Health improvements related to DDT use accounted for 21% to 56% of increased population growth in Guyana during the postwar years (5).

In summary, these data from South Africa, Sri Lanka, and Guyana are clearly contrary to the claims of Chen and Rogan (1) that ill effects of DDT on maternal health and infant survival would counterbalance the beneficial effect of malaria control. Their claim that alternative chemicals are cheaper than DDT is incorrect (8). Recent data on pyrethroid-treated bed nets are encouraging for situations in which sustained provision of spray pumps and trained spray teams are not feasible. However, even the best results with these nets do not match those obtained in the past with IRS, e.g., the suppression of malaria infection in Zanzibar from holoendemic levels to <5% (9).

In recent years, programs in South Africa and Madagascar (10) that again started IRS with DDT have greatly reduced malaria and malaria-related deaths. DDT is still needed and research is required to improve its use. The Stockholm Convention on Persistent Organic Pollutants specifically allows continued public health use of DDT.

Donald Roberts,*
Christopher Curtis,†
Richard Tren,‡ Brian Sharp,§
Clive Shiff,¶ and Roger Bate#

*Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA; †London School of Hygiene & Tropical Medicine, London, United Kingdom; ‡Africa Fighting Malaria, Sandton, South Africa; §Medical Research Council, Durban, South Africa; ¶Johns Hopkins University, Baltimore, Maryland, USA; and #Africa Fighting Malaria, Washington, D.C., USA

References

1. Chen A, Rogan WJ. Nonmalarial infant death and DDT use for malaria control. Emerg Infect Dis. 2003;9:960–4.
2. Bouwman H, Reinecke AJ, Cooppan RM, Becker PJ. Factors affecting levels of DDT and metabolites in human breast milk from Kwazulu. J Toxicol Environ Health. 1990;31:93–115.
3. Kornbrust D, Gillis B, Collins B, Goehl T, Bupta B, Schwetz B. Effects of 1,1-dichloro-2,2bis[p-chlorohenyl]ethylene (DDE) on lactation in rats. J Toxicol Environ Health. 1986;17:23–36.
4. Longnecker MP, Klebanoff MA, Zhou H, Brock JW. Association between maternal serum concentration of the DDT metabolite DDE and preterm and small-for-gestational-age babies at birth. Lancet. 2001; 358:110–4.
5. Newman P. Malaria eradication and population growth, with special reference to Ceylon and British Guiana. School of Public Health, Ann Arbor, Michigan, The University of Michigan, Bureau of Public Health Economics, Research Series No. 10. 1965; p. 259.
6. Giglioli G. Eradication of *Anopheles darlingi* from the inhabited areas of British Guiana by DDT residual spraying. J Natl Malar Soc. 1951;10:142–61.
7. Giglioli G. Changes in the pattern of mortality following the eradication of hyperendemic malaria from a highly susceptible community. Bull World Health Organ. 1972;46:181–202.
8. Walker K. Cost-comparison of DDT and alternative insecticides for malaria control. Med Vet Entomol. 2000;14:345–54.
9. Curtis CF, Mnzava AEP. Comparison of house spraying and insecticide-treated nets for malaria control. Bull World Health Organ. 2000;78:1389–400.
10. Romi R, Razaiarimanga A, Raharimanga R, Rakotondraibe EM, Ranaivo LH, Pietra V, et al. Impact of the malaria control campaign (1993–1998) in the highlands of Madagascar: parasitological and entomological data. Am J Trop Med Hyg. 2002;66:2–6.

Address for correspondence: Donald R. Roberts, Department of Preventive Medicine and Biometrics, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, MD 20814, USA; fax: 301-295-3731; email: droberts@usuhs.mil

In Reply: We do not believe that causality has been demonstrated for the relationship between dichlordiphenylethylene (DDE) and shorter period of lactation or preterm birth. However, we think the evidence is sufficiently strong that the possibility of causality cannot be dismissed and testing this hypothesis will require data from appropriately designed studies in areas where dichlorodiphenyltrichloroethane (DDT) is used.

We think that the cross-sectional study (1) referred to by Roberts et al. (2) cannot determine whether DDE shortens lactation. Women with higher levels of DDE and shorter lactation periods would be less likely than women with lower levels of DDE and longer lactation periods to appear in such a study, which would mask any associations.

As noted in the Longnecker report on the association between DDE and preterm birth (3), several previous studies have shown such an effect, but they were relatively small. That the perinatal collaborative study was not a random sample of U.S. births does not seem relevant. Women could not choose whether to participate on the basis of their DDT level because they did not know it and could not choose whether to participate on the basis of a preterm birth because they were enrolled during pregnancy.

Roberts et al. reference success stories of DDT use from the 1930s to

the 1950s in Sri Lanka and Guyana. The reports of the Sri Lanka study are not in the peer-reviewed literature. Data from the Guyana sugar plantations must include factors other than DDT and malaria because profound differences existed in all-cause mortality in adults and children over the span of the reports. Whether DDT was effective in those areas at that time cannot determine whether it would be a two-edged sword now.

Although the p,p′ isomer of DDE is in human tissue at the highest concentration, technical DDT contains approximately 10% of the o,p isomer, and o,p-DDE can be detected if sought (4). We and others measure p,p′-DDE as an index of total DDE, but our hypothesis for the estrogenic mechanism by which lactation time might be shortened involves the estrogenic isomer p,p'-DDE. The Kornbrust study of DDE and lactation in rodents used pure p, p-DDE, the most prevalent congener but also the least estrogenic one (5). Since the hypothesis concerned o,p-DDE, the estrogenic congener, the work was unfortunately noncontributory.

Malaria is a major public health problem, and vigorous efforts to prevent and treat it are necessary. We fear, though, that DDT is not entirely benign and have some evidence to show this. Proceeding as if the safety of DDT had been demonstrated absolutely does not seem a prudent course. DDT is inexpensive; however, cost is irrelevant if DDT use causes as many infant deaths as it prevents.

Aimin Chen* and Walter J. Rogan*

*National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA

References

1. Bouwman H, Reinecke AJ, Cooppan RM, Becker PJ. Factors affecting levels of DDT and metabolites in human breast milk from Kwazulu. J Toxicol Environ Health. 1990;31:93–115.
2. Roberts D, Curtis C, Tren R, Sharp B, Shiff C, Bate R. Malaria control and public health. Emerg Infect Dis. 2004;10:1170–1.
3. Longnecker MP, Klebanoff MA, Zhou H, Brock JW. Association between maternal serum concentration of the DDT metabolite DDE and preterm and small-for-gestational-age babies at birth. Lancet 2001; 358:110–4.
4. Jensen AA. Chemical contaminants in human milk. Residue Rev 1983;89:1–128.
5. Kornbrust D, Gillis B, Collins B, Goehl T, Gupta B, Schwetz B. Effects of 1,1-dichloro-2,2-bis[p-chlorophenyl]ethylene (DDE) on lactation in rats. J Toxicol Environ Health 1986;17:23–36.

Address for correspondence: Walter J. Rogan, Epidemiology Branch, National Institute of Environmental Health Sciences (NIEHS), P.O. Box 12233, Mail Drop A3-05, Research Triangle Park, NC 27709, USA; fax: 919-541-2511; email: rogan@niehs.nih.gov

CTX-M and Plasmid-mediated AmpC-Producing *Enterobacteriaceae*, Singapore

To the Editor: In gram-negative bacteria, β-lactamases are an important cause of antimicrobial resistance. In the 1990s, several new β-lactamases, including CTX-M type and plasmid-mediated AmpC β-lactamases, emerged.

CTX-M extended spectrum β-lactamases (ESBLs) differ from those derived from TEM and SHV enzymes by their preferential hydrolysis of cefotaxime and ceftriaxone compared with ceftazidime. They also differ from an evolutionary standpoint and are more closely related to the chromosomal enzymes of *Kluyvera* species (1). These enzymes are increasingly described worldwide, particularly in South America, Europe, and East Asia.

AmpC enzymes confer resistance to oxyimino- and 7-α-methoxycephalosporins. They occur naturally in the chromosomes of bacteria such as *Enterobacter*, *Citrobacter*, *Serratia*, and *Pseudomonas* species. In the last decade, genes coding for AmpC β-lactamases have made their way into plasmids and are increasingly detected in other species, notably *Klebsiella* and *Escherichia coli* (2).

We describe five strains of *Enterobacteriaceae* with unusual antimicrobial susceptibility patterns, which were isolated from patients in an 800-bed hospital in Singapore. *K. pneumoniae* EU17113, EU2673, and *E. coli* EU2657 were noted to be more susceptible to ceftazidime than ceftriaxone, whereas *E. coli* EU4855 and EB9505 were resistant to both cephalosporins. The National Committee for Clinical Laboratory Standards ESBL confirmatory test (3) was positive for strains EU17113, EU2673, and EU2657 but negative for strains EU4855 and EB9505. All strains were isolated from urine cultures except EB9505, which was isolated from blood culture. The isolates were identified by VITEK 2 (bioMérieux, Marcy l'Etoile, France) or Microbact 12E/A (Medvet Diagnostics, Thebarton, Australia).

The MICs by Etest (AB Biodisk, Solna, Sweden) and isoelectric points of β-lactamases in crude extracts are shown in the Table. Polymerase chain reaction (PCR) for CTX-M genes was performed on strains EU17113, EU2673, and EU2657 by using primers CTX-1 and CTX-2 as described by Pai et al. (4). This yielded an ≈780-bp product with DNA extracts from strain EU17113 but not the others. The sequence of this product was identical to $bla_{\text{CTX-M-9}}$ as found in the GenBank database (accession no. AJ416345.1). PCR was repeated for strains EU2673 and EU2657 with a different primer set as described by Gniadkowski et al. (5). This produced