MIXED BAG

Resistance to anti-flu drugs

With almost a promise that there will be another major influenza (flu) pandemic sometime soon, a paper in *The Lancet* makes uncomfortable reading. Several countries are already stockpiling anti-flu drugs in the hope that they can at least ameliorate the effects of the virus when it hits. Adamantane derivatives, such as amantadine and rimantadine, have been used successfully for the prevention and treatment of influenza A virus infections for more than a decade. Human and animal studies have shown frequent amantadine resistance in influenza viruses after exposure to the drug and drug-resistant viruses can by transmitted between people without any apparent loss of pathogenicity. However, since 1991, drug-susceptibility surveillance has been carried out routinely in influenza virus isolates submitted to the WHO Collaborating Center for Influenza at the US Centers for Disease Control and Prevention. The available studies have shown very low levels of resistance to these drugs among circulating influenza viruses. But, their use is increasing worldwide and drug resistance has been reported among influenza A (H5N1) viruses isolated from poultry and people in Asia and 10 years have passed since the last comprehensive global study of resistance to these drugs was published.

The authors analysed data for influenza field isolates that were obtained around the world and submitted to the WHO Collaborating Centre for Influenza between 1 October 1994 and 31 March 2005. Using pyrosequencing, confirmatory sequence analysis and phenotypic testing, the authors looked for drug resistance among circulating influenza A H3N2, H1N1 and H1N2 viruses. They screened more than 7 000 influenza A field isolates for drug resistance. During the 10 years of surveillance they found a significant increase in drug resistance – from 0.4% in 1994 - 1995 to 12.3% in 2003 - 2004. Most of the resistant viruses found since 2003 were found in people in Asia.

These data obviously raise concerns about the use of adamantanes and how important it is to continue to track the emergence and spread of drug-resistant influenza A viruses.

Bright RA, *et al. Lancet* 2005; **366:** 1175-1181.

TB drug resistance and HIV in Botswana

Tuberculosis (TB) and HIV are now running as parallel epidemics in most of southern Africa and the rising incidence of drug-resistant TB in South Africa in particular is already causing concern. TB is the single most common opportunistic infection among those infected with HIV in the region and an equally common cause of death from AIDS.

In Botswana, the incidence of TB in 2002 was 623 cases per 100 000 people, according to a recent research letter in *The Lancet*. The last 2 surveys of antituberculosis drug resistance in Botswana were undertaken in 1995, 1996 and 1999 and showed low levels of resistance despite a three-fold increase in TB since 1989. Botswana started 100% coverage of the DOTS (directly observed short course) strategy in 1986, including a 6-month regimen for all patients; treatment consisting of 2 months of isoniazid, rifampicin, pyrazinamide and ethambutol, followed by 4 months of isoniazid and rifampicin. Streptomycin was only included in re-treatment regimens. In 2002, the case detection rate in Botswana was 88%, of which 78% of patients successfully completed treatment and 6% interrupted treatment.

Turning to HIV, the authors report that in 2003 HIV prevalence in pregnant women aged 15 - 49 in Botswana was 37%. In the first survey of TB drug resistance, of the 44% of patients with TB who agreed to HIV testing, 49% were infected. More recent research suggests that more than 80% of patients with TB in hospital have HIV as well. So far, surveillance of TB patients for HIV infection has been anonymous.

The authors started a third survey looking at trends in antituberculosis drug resistance in patients with TB in 2002. They also used a rapid test of HIV infection (Oraquick) to estimate HIV infection in these patients. From 15 March 2002 they took samples from 2 425 consecutive patients. They identified 1 457 samples as positive for HIV. Assuming that all or none of the 219 patients with smear-negative sputum samples were HIV infected would give a range of 56 - 66% HIV prevalence in those with confirmed TB. Of the 2 425 patients, 1 481 had sputum-positive TB. Of these, 1 288 had culture-positive TB and also had complete drug-susceptibility test results and information on previous treatment status. Thirty-two patients had non-tuberculosis mycobacteria, 1 182 were new patients, and 106 had previous treatment for TB.

Resistance testing indicated a rise in antituberculosis drug resistance and HIV prevalence of 60% in patients with TB. These data are from a country that has the highest incidence of TB and HIV-associated TB in sub-Saharan Africa. This means that the increasing trend for multidrug-resistant TB in Botswana has important implications for TB control and HIV treatment and care. There is evidence to suggest that a large proportion of TB in HIV-positive patients in areas with a high prevalence of both diseases could be due to new infections rather than reactivation of latent infection. The increase in drug-resistant strains of TB in Botswana in new patients with TB suggests increasing transmission of drug-resistant strains in the community. This could be caused by increased treatment interruption or poor treatment compliance. Factors such as malabsorption in HIV-positive patients with TB could also contribute to acquired rifampicin resistance. Unfortunately, because HIV testing was anonymous, the authors could not look for any link between HIV status and drug-resistant TB.

The authors suggest that national programmes for isoniazid prophylaxis and antiretroviral therapy need to be expanded to help reduce the number of people with TB. But, they also point out that patients must be carefully screened for TB in case they receive only isoniazid, which could further increase drug resistance. Furthermore, they recommend increased TB case finding, control of TB transmission in settings such as hospitals and prisons and case management to ensure that treatment is successfully completed.

The burden of TB and HIV across southern Africa obviously has serious implications for public health interventions generally. These findings are important and must not be ignored.

Nelson LJ, *et al. Lancet* 2005; **366:** 488-490.

Treating cholera in children

Cholera, caused either by *Vibrio cholera* O1 or O139, is a major health problem around the world, particularly in children in cholera-endemic areas in the developing world. Between 120 000 and 150 000 cases are reported annually, of which 80% are in Africa. A recent paper in *The Lancet* discusses the treatment of cholera in children. Debasish Saha and colleagues point out that treatment with an effective antimicrobial drug reduces the volume and duration of cholera-related diarrhoea by half, and is an important adjunct to fluid treatment. This reduction in fluid needs leads to reduced time in hospital, reduced demands on health care systems and lower costs – all important considerations in resource-poor settings. This is particularly important in epidemics of the disease, where health services may be seriously overloaded.

The usual treatment for cholera includes 3 - 5 days of antimicrobial treatment. World Health Organization recommendations are for a 3-day, 12-dose course of either tetracycline or erythromycin for treating the disease in children. However, single-dose therapy with doxycycline is well established in adults and, more recently, single-dose ciprofloxacin has been shown to be effective in adults. Children have been assessed with single-dose furazolidone and azithromycin, the latter proving effective. As the authors point out, antimicrobial resistance in *V. cholerae* O1 and O139 limits treatment options, specifically co-trimoxazole and tetracycline resistance. Tetracyclines are also not recommended in children because of problems with toxicity and have not been widely used to treat cholera in children.

Saha and colleagues set out to assess whether a single dose of ciprofloxacin would be as effective as a 3-day, 12-dose course of erythromycin in achieving clinical cure in children with severe cholera. They conducted a randomised, open-label, controlled trial in children aged 2 - 15 years with proven cholera. The children received either a single 20 mg/kg dose of ciprofloxacin or 12.5 mg/kg of erythromycin every 6 hours for 3 days and remained in hospital for 5 days. They assessed efficacy according to stopping of watery stools within 48 hours of starting drug treatment.

Treatment was clinically successful in 60% of the children treated with ciprofloxacin and in 55% of those treated with erythromycin. The children who received ciprofloxacin also vomited less frequently, had fewer stools and less stool volume than those receiving erythromycin. However, bacteriological failure was more common in those treated with ciprofloxacin than in those treated with erythromycin.

The conclusion was that single-dose ciprofloxacin achieves clinical outcomes similar to, or better than, those achieved with 12-dose erythromycin, although it is less effective at eliminating *V. cholerae* from the stool. The authors suggest that because both ciprofloxacin and azythromycin have been shown to be effective clinically they should be considered as first-line options for treating childhood cholera in areas where cholera is caused by susceptible strains of *V. cholerae*.

Saha D, *et al. Lancet* 2005; **366:** 1085-1093.

Bridget Farham