Amantadine prophylaxis for health care workers: unanswered questions

In November 1989 the United Kingdom experienced its largest epidemic of influenza A for thirteen years. A sudden, marked increase in the indices for influenza surveillance was followed by reports in national and local media of outbreaks in schools, hospitals and homes for the elderly. Many hospitals were forced to postpone admissions for elective surgery, as emergency admissions increased and large numbers of staff succumbed to influenza.

Is there therefore a place for influenza prophylaxis for health care staff? Health care workers in close contact with high risk persons are regarded as a target group for vaccination in the USA (Recommendations of the Immunization Practices Advisory Committee (ACIP), 1990) but vaccination is not currently recommended for this group in the UK (Department of Health (UK), 1990).

In recent years enthusiasm for vaccination has declined, partly because of the need for annual vaccination, and the practical and social difficulties associated with this (Tyrrell & Smith, 1979) but mainly because of doubts about the long term efficacy of such a system (Hoskins et al., 1979).

The use of vaccine to control influenza in a health care setting would also be relatively expensive. For my own 600-bedded acute hospital I have calculated that, at current prices (approximately £5 per dose), the cost of vaccine alone for 'key staff' would be £5000.

The other potential prophylactic agents are the antiviral drugs, amantadine and rimantadine. Rimantadine is not available in the USA or the UK but amantadine has been licensed since 1966 for the prophylaxis of influenza A. It is still widely used to control the symptoms of Parkinson's disease and is thus readily available in the event of an epidemic of influenza. It has been shown to be effective in the prophylaxis and treatment of influenza A in boarding schools (Payler & Purdham, 1984) and in community studies (Dolin et al., 1982). However, two studies where the drug was given to household contacts of index cases gave conflicting results (Galbraith et al., 1969a, b).

In the USA the Immunization Practices Advisory Committee (IPAC) of the Centers for Disease Control (CDC) provides specific guidelines for the use of amantadine in those health care staff who have close contact with high risk patients (Imperato, 1986). The most recent UK guidelines (Department of Health (UK), 1990) mention that the prophylactic use of amantadine should be considered in the management of outbreaks of influenza but give no indication of the circumstances in which such a strategy should be adopted. This is a reflection of the dearth of information on the use of this drug in a health care setting. In the UK this may be due to the absence of any sizeable epidemic of influenza A for thirteen years.

Amantadine is only effective against influenza A, so widespread prophylaxis for health care staff would only be appropriate if it could be shown that influenza A virus was present locally. The availability of specific monoclonal antibodies capable of detecting influenza A virus in respiratory specimens means that, in theory, rapid diagnosis can be undertaken in any district general hospital laboratory (McQuillin, Madeley & Kendal, 1985). Some of these laboratories already provide a diagnostic service for respiratory syncytial virus, which uses a monoclonal antibody to detect virus in nasopharyngeal aspirates obtained from sick infants. Therefore they already have the expertise necessary to obtain adequate specimens and for the preparation, performance and interpretation of the immunofluorescent test.

Obtaining nasopharyngeal aspirates from older children and adults is a more daunting undertaking, but a single individual, such as an infection control nurse, could be taught the appropriate technique. Impression smears or tissue suspensions of post mortem lung tissue are additional sources of material for rapid viral diagnosis.

The organisational aspects of offering amantadine prophylaxis to healthy 'key' personnel are formidable. The definition of 'key' personnel is open to many interpretations.
Nurses involved in direct patient care are probably the largest group. Whether all nurses would receive prophylaxis, or only those who have the highest risk of exposure (such as those working on medical, geriatric and paediatric wards) would have to be determined in advance. Medical staff are an essential group, particularly as illness may cause havoc with on-call rotas and locums may not be available at short notice. Other, smaller groups such as switchboard operators and pharmacy staff should be considered. How long should amantadine prophylaxis be given? During a boarding school outbreak boys were given a fourteen-day course of amantadine, prophylaxis being initiated nine days after the first case of influenza A (Payler & Purdham, 1984). Hayden et al. (1989) gave rimantadine for ten days to household contacts of index cases and Dolin et al. (1982) gave the drug for six weeks to volunteers in a community outbreak. In a hospital setting, prolonged prophylaxis would be difficult to sustain and would add to the cost.

The best strategy might be to aim for a short course of three to seven days 'to buy time' while an epidemic was at its peak. This would protect essential staff for long enough to allow those who were already ill time to recover and return to work. Such a strategy would require a decision to initiate prophylaxis at some predetermined level of sickness absence. This might lead to serious problems with compliance. While this intervention could be discussed with those senior staff involved before an influenza epidemic, it might be many years before a sufficiently large epidemic of influenza A occurred to warrant intervention. Those who originally formulated the plan might not be present to implement it at the time of an epidemic.

Staff would need to be warned of side effects. Quite possibly healthy individuals would be unwilling to accept prophylaxis intended to keep them at work when the side effects — nervousness, inability to concentrate, insomnia and dizziness — might impair their ability to work. However, a virtual absence of side effects was recorded when a dose of 100 mg amantadine daily was used (Payler & Purdham, 1984) compared with the withdrawal of 13% of patients because of side effects when 200 mg daily was given by Dolin et al. (1982). Staff could be given a small supply of amantadine to take if they experienced symptoms which heralded the onset of influenza. Such a strategy could be extremely useful for medical staff approaching a night or weekend on duty. It would also be comparatively cheap. The cost of a five day course of a single daily dose of 100 mg amantadine is approximately £0.70.

There remains the concern that widespread use of amantadine for prophylaxis and treatment might result in nosocomial transmission of resistant strains of influenza A virus. Transmission of drug-resistant strains of virus has recently been reported in a nursing home where amantadine failed to control an outbreak (Mast et al., 1989). The emergence and apparent transmission of rimantadine-resistant influenza A has also been observed when that drug was given to prevent transmission within families (Hayden et al., 1989).

Clearly there is an urgent need for further studies to answer some of these questions. Most importantly, we need to know whether amantadine will protect health care workers when given for short periods. Until we have that information it will be difficult for hospitals to adopt an effective strategy to maintain services during the next influenza epidemic.

References
isms. In 1990, around 10% of non-capsulate /Mactamase production among type b organ-
el al., 1988), the capsulated strains (Machka et al., 1989). In addition, since Tudor-Williams capsulated strains) infections (Makela, 1988; Holmberg et al., 1988). The prevalence of resistance to several anti-
microbial agents among encapsulated strains (> 90% due to type b encapsulated strains) and non-invasive (predominantly due to non-
capsulated strains) infections (Mäkelä, 1988; Tudor-Williams et al., 1989). In addition, since the prevalence of resistance to several anti-
microbial agents among encapsulated strains of type b is often higher than that among non-
capsulated strains (Machka et al., 1988), the likelihood of an infection being due to a type b strain has become an important consideration when deciding on treatment while awaiting results of culture and susceptibility tests. A consistent finding in national and international surveys of antimicrobial resistance in H. influenzae has been the higher prevalence of /-lactamase production among type b organ-
isms. In 1990, around 10% of non-capsulate isolates from England and Scotland were found to be /-lactamase-positive (unpublished data) compared with 25% of type b organisms from blood and CSF specimens in 1986 (Powell et al., 1987). Similarly, 8% of non-
capsulate and 13% of type b H. influenzae from Wales in 1986 produced /-lactamase (Howard & Williams, 1988). Corresponding figures in Ireland in 1988 were 10% and 17% (Howard & Williams, 1989). The highest prevalence rates recorded in Europe in 1986 were 26% and 17% in Belgium and 64% and 26% in Spain among type b and non-capsu-
lated strains, respectively (Machka et al., 1988).

In contrast, ampicillin-resistant (MIC = 1 mg/l) /-lactamase-negative H. influenzae are very predominantly non-capsulated organisms isolated from sputum. Reports of similar type b organisms that have produced invasive infections have been rare (Offit, Campos & Plotkin, 1982). These isolates frequently show broad-spectrum reduced susceptibility to several other /-lactams, but not usually to the carbapenems (Powell, Seetulsingh & Williams, 1989). The prevalence of this type of resistance was 4% in England and Scotland and 6% in the USA in 1986 (Powell et al., 1987; Doern et al., 1988).

As a result, amoxycillin, with or without clavulanate, appears unlikely to be successful against organisms which have non-enzyme-
mediated resistance to ampicillin, although the combination of amoxycillin with clavulanate has proved to be very useful in treating infec-
tions associated with /-lactamase-positive organisms (Wallace et al., 1985). Reported activities of newer combinations with enzyme inhibitors (e.g. sulbactam or tazobactam) suggest that these are also likely to be affected by mechanisms involved in non-
/-lactamase-mediated resistance (Simonet et al., 1989). Similarly, the orally-administered cephalos-
porins cefaclor, cephalexin and cefuroxime (as axetil), which are not very active against H. influenzae (modal MICs of 2, 8 and 0.5 mg/l respectively), are unlikely to retain useful activity against organisms possessing intrinsic resistance to /-lactams (Philpott-Howard & Williams, 1983).

Resistance to chloramphenicol varies between 1% and 4% among type b and non-
capsulated H. influenzae in the UK (Powell et al., 1987; Howard & Williams, 1989) and is now more common among type b than non-
capsulated H. influenzae in several countries (Machka et al., 1988). Although chloram-
phenicol-resistant type b strains associated