CASE STUDIES

Case study 1

Background

Access to treatment following clinical trials: the case of a pneumococcal conjugate vaccine trial in the Gambia.

Acute lower respiratory infections (ALRI) are a major cause of morbidity and death in Gambian children. Approximately 1 in 25 rural Gambian children dies from an ALRI before the age of 5. Studies of the aetiology of ALRI, carried out both in hospital and in the community, have shown that pneumococcus is the most important cause of severe ALRI in Gambian children, accounting for approximately 5%-10% of total cases of severe ALRI. Thus, prevention of this infection is a priority. Vaccination offers the most promising means of achieving this objective in the short to medium term.

In previous vaccine trials, Gambian infants have responded poorly to immunisation with a pneumococcal polysaccharide vaccine. However, children of the same age have responded well to pneumococcal polysaccharide/protein conjugate vaccines, which have also been shown to induce immunological memory. Thus, there are good grounds for believing that a pneumococcal conjugate vaccine, which covers the majority of serotypes of pneumococci prevalent in the Gambia, could reduce the incidence of invasive pneumococcal disease in young children substantially and thus lower childhood mortality from ALRI.

A randomised, controlled trial of a nine-valent pneumococcal conjugate vaccine is proposed to investigate this hypothesis. The main endpoint of the trial will be overall mortality; secondary end-points will include the effect of the vaccine on mortality from AIRI and on invasive pneumococcal disease caused by pneumococci of vaccine serotype. Over a period of three and a half years, approximately 45,000 children will be recruited into the trial.

During a six-month period before vaccination commences, all households in the study area will be mapped. All infants resident in the study area will be eligible to join the trial when they present for their first diphtheria/pertussis/tetanus/haemophilus *influenzas* type b (DPT/Hib) vaccine at the age of about two months. After informed consent has been obtained from their parents or guardian, infants will be randomised individually to receive at the ages of 2, 3 and 4 months three doses of DPT/Hib vaccine mixed with a nine-valent pneumococcal conjugate vaccine produced by Wyeth Lederle Pediatrics (types 1, 4, 5, 68, gv, 14, 18C, 19F, and 23F polysaccharides) or DPT/Hib alone. Other vaccines will be given according to the routine EPI schedule. Deaths among study children will be detected using a system of village reporters resident in each village in the study area and through regular three-monthly visits to each study child. Cause of death will be ascertained using the verbal autopsy technique. All study children who present to designated hospitals/health centres with an illness suggestive of meningitis, pneumonia or septicaemia will be investigated for possible invasive pneumoccocal disease by blood culture and other appropriate investigations.

Based on information obtained previously in children in the study area it is estimated that the trial will be powered adequately to detect a 9% reduction in overall mortality, a 30% reduction in mortality due to an ALRI, a 10% reduction in ALRI, a 30% reduction in the incidence of radiological pneumonia and an 80% reduction in the incidence of invasive disease due to pneumococci of vaccine serotype.

A data and safety monitoring board and an international steering committee will be established to monitor the trial. It is anticipated that it will take approximately 5 years and three months to

complete. However, three months before vaccination is scheduled to be completed, an interim review will be undertaken to determine whether continuation of vaccination or surveillance for an extra few months would improve substantially the trial's chances of achieving its endpoints.

Because of its ability to produce high serotype-specific antibody concentrations in infants, the vaccine is expected to be most useful in younger children. The proposed trial will not provide specific data on the vaccine's efficacy in older children. However, the question will certainly arise following the trial of whether the findings (assuming they are positive) are generalizable to older children, i.e. whether the findings will support vaccination of older children. In addition, one of the main ethical issues is whether children in the control group should be given the opportunity to receive the study vaccine, either during the trial (e.g. at age 2 or 3 years) or following its completion?

This decision is complicated by a range of factors that could have a strong bearing on vaccine research and public health policy in The Gambia. The vaccination of controls would mean the loss of potentially useful comparative information on the long-term effects of vaccination. The non- vaccination of controls would mean either setting up potentially expensive ($1million/yr.) monitoring arrangements to gauge long-term effects of control ,versus test groups; or a decision not to follow-up on differences in outcomes between the two groups on the grounds that money would be better spent in other ways. And finally, because of the double-blind design of the trial, the status of any individual child in the study (vaccine or control) would be unknown until the end of the trial. Therefore, vaccination of trial participants in an attempt to ensure vaccination of controls at any point during the trial would mean that half the children would be vaccinated twice. Given the complexity of the situation described above, the option of post-trial vaccination of controls was initially favoured. However, the uncertainty about the applicability of the study findings to children in the control arm (who will be 5 years of age at the end of the trial) has required looking for alternative approaches that are fair and scientifically sensible. .

Questions

You are the representative of the Gambian Ministry of Health responsible for this trial. A proposal has recently been made to you by the study investigators that a reasonable approach would be to offer the option of vaccination to younger siblings of children in the control group, rather than the controls themselves, since the younger children are better vaccination candidates? In preparation for your up-coming meeting with the investigators you are considering the following questions.

Specific Questions
(i) Is this a reasonable idea? Why or why not?
(ii) Should the vaccine be made available to only one sibling? Is it reasonable to ask parents to choose which of their children should be vaccinated?
(iii) What about children who don't have younger siblings?
(iv) Should the control group have "first claim" on the vaccine after completion of the trial, either for themselves, or for their families?

Bibliography

1. Mulholland K, Usen S, Adegbola R, Weber M. Use of pneumococcal polysaccharide vaccine in children. Lancet 1998; 352(9127): 575-6.

2. Usen S, Adegbola R, Mulholland K, Jaffar S, Hilton S, Oparaugo A, Omosigho C, Lahai G, Corrah T, Palmer A, Schneider G, Weber M, Greenwood B Epidemiology of invasive pneumococcal disease in the Western Region, The Gambia. Pediatr Infect Dis J. 1998; 17(1): 23-8.

3. O'Dempsey TJ, McArdle TF, Lloyd-Evans N, Baldeh 1, Lawrence BE, / v 5ecka 0, Greenwood

B. Pneumococcal disease among children in a rural area of west Africa. Pediatr Infect Dis J. 1996; 15(5): 431-7.

4. Leach A, Ceesay SJ, Banya WAf Greenwood BM Pilot trial of a pentavalent pneumococcal polysaccharide/protein conjugate vaccine in Gambian infants. Pediatr Infect Dis J 1996; 15 (4): 333-9.

5. Greenwood B. Epidemiology of acute lower respiratory tract infections, especially those due to Haemophilus influenzae type b, in The Gambia, west Africa. J Infect Dis 1992; 165(SuppI1): 526-8.

6. King N. Defining and describing benefit appropriately in clinical trials. Journal of Law, Medicine & Ethics 2000; 28: 332-343.

7. Glantz L, Annas G, et al. Research in developing countries: taking "benefit" seriously. Hastings Center Report 1998; 28(6): 38-42.

8. Benatar SR, Singer PA. A new look at international research ethics. BMJ 2000; 321: 824-6.

9. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? JAMA 2000; 283: 2701-2711.

Case study provided by MRC (U.K.)