Should patients positive for HIV infection receive pneumococcal vaccine?

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Pneumococcal vaccination effectively reduces the incidence of invasive pneumococcal disease in normal subjects. Such invasive pneumococcal disease is 100 times more common in patients with HIV infection than in healthy people, so it seems logical to target this group of patients for vaccination. Few clinics routinely vaccinate patients positive for HIV, despite Department of Health guidelines. This is because of uncertainty about the vaccine's efficacy in HIV disease. There are many reasons to suspect that the vaccine will fail to protect these patients, including the fact that antibodies alone may not be sufficient protection against all serogroups of *Pneumococcus* and the vaccine works in healthy people but not immunocompromised subjects. Vaccination of HIV positive patients may not be indicated, at least for the time being. The cost of vaccinating such patients in the absence of data showing efficacy may well be less than the cost of a necessarily large and lengthy trial. But the truth must be sought to end current indecision.

Prophylaxis against many opportunistic infections in patients positive for HIV infection has deservedly become routine clinical practice; clinicians continue to be divided on whether it should include pneumococcal vaccination. No consensus exists in the United Kingdom or the United States, each country espousing different policies. The incidence of pneumococcal bacteraemia in people with AIDS is 9.4 per 1000 person years annually—a several hundredfold increase over that in an age matched population without such infection.¹ In a study from California five out of 41 (12%) patients with community acquired pneumococcal bacteraemia were subsequently found to be seropositive for HIV; Chirugi *et al* suggested that for their community this presentation was common enough to be an indication for HIV testing.² Mortality from pneumococcal disease in HIV positive patients remains substantial and varies from 5% to 20%; 20% mortality is higher than that in an age matched control group.³

Prompted by several trials demonstrating vaccine protective efficacy in large numbers of patients,^{4,5} the American Immunization Practices Advisory Committee has recommended that HIV positive children of 2 years and over, and adults with symptomatic or asymptomatic HIV infection, should be vaccinated⁶; similar recommendations have also been published in Norway.⁸ The British guidelines recommend that pneumococcal vaccination should be considered for those aged over 2 years in whom pneumococcal infection is likely to be more common and dangerous—that is, those who are immunodeficient or immunosuppressed through treatment or disease, including HIV infection at all stages.⁹

Are such recommendations implemented, or even justified, in the United Kingdom? We asked 12 randomly selected clinics from the Greater London area whether they were routinely vaccinating their HIV positive patients at any stage of disease. Only one clinic, which dealt with haemophilic patients, was

Clinical observation of outcome persuaded Jenner that his vaccine would work

doing so. Consultant staff at the remaining 11 clinics replied that they had considered the issue but had not arrived at a policy that addressed why these guidelines were not being locally implemented. This poor take up rate probably relates to uncertainty about the value of immunisation in this group of patients. Issues that need to be investigated are (a) whether HIV positive patients can mount an effective antibody response; (b) whether the antibody response can be boosted by vaccination; (c) whether the pneumococcal serotypes responsible for invasive disease are present in the vaccine; and (d) whether pneumococcal antibodies protect against invasive disease.

Antibody response to pneumococci and efficacy of vaccination in HIV positive patients

Pinching¹⁰ reviewed published reports on the ability of HIV positive patients to generate antibody responses to protein and polysaccharide antigens. Most groups found low titres of pneumococcal antibody before vaccination, with a variable but substandard rise in titres after vaccination and clinical evidence of vaccine failure.¹¹⁻¹³ This finding was confirmed and extended by Janoff *et al*, who found that antigen specific antibody titres waned as AIDS progressed¹⁴; Rodriguez-Barradas *et al* found that antibody responses to pneumococcal polysaccharide could be classified according to clinical disease stage and CD4 positive cell count.¹⁵ Thus, HIV positive patients with a CD4 positive cell count of $>500 \times 10^6/l$

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generated antibody responses to vaccine indistinguishable from a matched group of healthy men with no known risk factors for HIV; responses in those with lower CD4 positive cell counts were significantly reduced. Such findings are in stark contrast to those of Kroon *et al*¹⁵ who found no relation between CD4 count and antibody concentrations after vaccination. Additionally, Glaser *et al* found that patients with CD4 positive cell counts of $<200 \times 10^6$ who were receiving concurrent zidovudine treatment had as effective a response to vaccination as HIV positive patients who were free of symptoms.¹⁶ They suggested that zidovudine therapy should be initiated four weeks before proposed vaccination.

Unfortunately, however, the study of Unsworth *et al* found that only half of an HIV positive cohort showed an appreciable IgG₂ subclass response to pneumococcal vaccine, the extent of the response being unrelated to CD4 count.¹⁷ IgG₂ antibodies are preferentially synthesised in response to polysaccharide antigens,¹⁸ and it is particularly important in the control of pyogenic infection in normal people.¹⁹ Even more importantly, this antibody subclass is significantly depressed in patients with AIDS or AIDS related complex who have developed pyogenic infection.²⁰ Thus a pragmatic policy of early vaccination, when HIV infection is first diagnosed, or even earlier in seronegative but high risk groups,^{14,15} is reasonable, but the subjects who will respond favourably to the vaccine are as yet unidentifiable and why they should respond is unknown.

Presence of pneumococcal serotypes responsible for invasive disease in vaccine

Pneumococcal vaccination protects against only its constituent strains. It is therefore important to know whether the 23 serotypes contained within the vaccine cause clinical disease. In a study of 75 episodes of pneumococcal bacteraemia in HIV positive residents of San Francisco, Redd *et al* found that 82% of the strains responsible were represented in the currently available vaccine.¹ Though we could find no equivalent British data, all the serotypes responsible for 14 cases of pneumococcal bacteraemia in HIV positive patients in St Thomas's Hospital were present in the vaccine.

Efficacy of pneumococcal antibodies against invasive pneumococcal disease

Protection against pneumococci probably entails more than simply antibodies. When investigating the protective effects of pneumococcal vaccination in a population of healthy adults and elderly patients with bronchitis Musher *et al* found no relation between the ability of serum to opsonise pneumococci and specific antibody titres.²¹ Furthermore, antibody responses in a cohort of hypogammaglobulinaemic patients did not correlate with severity and frequency of infection.²² Hamilos *et al* similarly found that the frequency of episodes of bronchitis and sinusitis (particularly prevalent in HIV disease, and perhaps another manifestation of pneumococcal disease in some cases) was not linked to specific antibody production.²³ The evidence that presence of a certain minimum titre of antibody, irrespective of class, protects against naturally (as opposed to experimentally) acquired human pneumococcal disease is therefore lacking.²⁴

But what of the large trials that show protective efficacy? Shapiro *et al* showed a 61% protective efficacy in immunocompetent patients and an insignificant effect (21% efficacy (95% confidence interval -55% to 60%)) in patients who were immunosuppressed for

reasons other than HIV infection.²⁵ This suggests that extrapolation from those trials recruiting immunologically normal people, or not specifically asking the question in an HIV positive cohort, may not be appropriate. Furthermore, vaccination does not influence carriage rate in normal subjects²⁶; it is most unlikely to do so in HIV positive subjects. Occasional invasive disease in healthy subjects may relate to a low, or absent, titre of type specific antibody; these people may simply be immunologically naive for that particular strain, and the vaccine pre-empts this deficiency and is therefore protective. The increased predisposition of HIV positive patients to pneumococcal disease may result from an unrelated and acquired defect in innate (as opposed to acquired humoral) immunity, for which the vaccine cannot be expected to be effective. For example, increased susceptibility may be at least partly the result of HIV induced abnormalities of phagocyte function, such as chemotaxis²⁷ and phagocytosis,²⁸ although experimental evidence for phagocytosis is lacking for *Streptococcus pneumoniae*. Bloodstream clearance of antibody coated particles mediated by Fc receptors is abnormal in AIDS,²⁹ and this may explain the higher rate of pneumococcal bacteraemia in seropositive patients with pneumonia.³⁰ Until more is known about how pneumococcus invades to cause disease, and what elements of natural immunity contribute to its control, it seems premature to assume that enhanced anti-pneumococcal polysaccharide antibody concentrations in HIV positive patients will automatically lead to enhanced protection. Furthermore, several serogroups are particularly associated with invasive disease in normal early childhood, suggesting that antibody responses to some but not all serogroups are dependent on a mature, functional T cell network.^{30a} In conclusion, we do not know whether pneumococcal vaccination is effective in this patient group, let alone whether such efficacy extends to some, or all, serogroups.

Options other than vaccination

Clinicians may consider prophylactic antibiotics as an alternative to vaccination. The current use of co-trimoxazole as prophylaxis against *Pneumocystis carinii* pneumonia is unlikely to confer equivalent protection against pneumococci, especially as lower and less frequent doses currently tend to be given. Although the drug is active in vitro against susceptible strains, high levels of resistance to the antibiotic have been documented in the community,³¹ and there also remains the question of efficacy in secretions.³² Daily penicillin for life may well be effective, but it is one more drug to take and increases the number of potential side effects.

Streptococcus pneumoniae has more than 80 serotypes. Protection against all serotypes probably entails more than just antibodies

The issue of a clinical trial of vaccine efficacy arises, and the sheer size of the American trials, essential for valid interpretation, should be borne in mind. A theoretical cost-benefit analysis in the United States has been based on the assumption that pneumococcal polysaccharide antibodies confer disease protection. The analysis showed net savings even if vaccination efficiency was only 10% of that in normal subjects and the duration of protection was substantially reduced,³³ as might be expected in HIV disease. This important theoretical cost benefit analysis should be balanced against the cost of a lengthy trial of sufficient size to achieve statistical power, which would settle the question once and for all. Currently 20 000 patients in the United Kingdom are positive for HIV, with countless more unaware of their HIV status³⁴; to vaccinate these would cost approximately £240 000. Data from trials suggest that the vaccine works in healthy but not immunosuppressed people—yet we continue to vaccinate those who will benefit the least. The trials show that if we are to vaccinate anyone, it should be this country's healthy population. Until we know more about the state of immunological health in early HIV disease, it continues to be illogical to consider vaccinating all or some HIV positive patients, especially in the light of the imminent arrival of conjugate vaccines, whose properties and serogroup composition may well differ from the currently available preparation. Furthermore, the intricacies of mucosal immunity and its breakdown in HIV disease are little understood; currently the only way to determine whether vaccination is worth while is to perform a trial of considerable size for statistical reasons. What price truth?

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ONE HUNDRED YEARS AGO

THE REMUNERATION OF NURSES.

A perusal of the recently published annual report of the Guy's Hospital Trained Nurses' Institution may well make the reader, who remembers his Virgil, apply with the needful difference a certain quotation on the blessedness of husbandmen ("O fortunati nimium, sua si bona norint") to those nurses who are employed on the private nursing staff at Guy's. We learn that in the twelve months ending December 31st last, there have been from 82 to 85 of these nurses at work, that they have earned close upon £6,000, have nursed 832 cases, have refused 120 applications, have added £250 to the reserve fund, now standing at £1,000, and have withal had £500 divided amongst them by way of bonus. In the case of the senior

nurses this bonus reaches the sum of £80, in addition to a salary of £40 per annum and all found. Last year we gave prominence to the scheme for profit sharing then introduced, and to the plan whereby the bonus additions were invested with the Royal National Pension Fund for Nurses to provide superannuation allowances at the age of 55 years. The Treasurer states that the arrangement has met with wide approval, and "has without doubt attracted the patronage of medical men throughout the country." The fact that, in a year which has been characterised in general by a slackened demand for nurses, such excellent results should have been attained by this institution appears to bear out the opinion thus expressed.

(*BMJ* 1895;ii:650.)