Papers

Immune response to a new hepatitis B vaccine in healthcare workers who had not responded to standard vaccine: randomised double blind dose-response study

Jane N Zuckerman, Caroline Sabin, Fiona M Craig, A Williams, Arie J Zuckerman

Abstract

Objective: To evaluate the immunogenicity and reactogenicity of a new triple S recombinant hepatitis B vaccine in a cohort of healthy people in whom currently licensed hepatitis B vaccines had persistently not induced an immune response.
Design: Single centre, randomised, double blind, dose-response study.
Setting: Research vaccine evaluation centre at a teaching hospital.
Subjects: 100 healthcare workers aged 18-70 years with a history of failure to seroconvert after at least four doses of a licensed hepatitis B vaccine containing the S component.
Intervention: Each subject was randomly allocated two doses of 5, 10, 20, or 40 μg of a new hepatitis B vaccine two months apart.
Main outcome measures: Immunogenicity of the four doses. Seroconversion and seroprotection were defined as an antibody titre >10 IU/l and >100 IU/l respectively against an international antibody standard.
Results: 69 subjects seroconverted after a single dose of the vaccine. After the booster vaccination one other subject seroconverted, bringing the overall seroconversion rate to 70%. Fifteen subjects given 5 μg of vaccine, 19 given 10 μg, 16 given 20 μg, and 20 given 40 μg seroconverted. Seroconversion rates in the four antigen dose groups were 60% (15/25), 76% (19/25), 64% (16/25), and 80% (20/25). After the booster dose there was no significant dose-response effect on the overall seroconversion rate, although the small sample size meant that a clinically important dose-response could not be ruled out.
Conclusion: A single dose of 20 μg of the vaccine was as effective as two doses of either 40 μg or 20 μg of this vaccine formulation in terms of seroconversion, seroprotection, and geometric mean titres.

Introduction

Hepatitis B and its sequelae, which include chronic liver disease, cirrhosis, and hepatocellular carcinoma, is a major public health problem throughout the world. Many millions of people are estimated to become infected every year worldwide, and about 350 million chronic carriers constitute the primary reservoir of infection. Hepatitis B is transmitted primarily by blood to blood contact as well as sexually.

Systematic vaccination of individuals at risk of exposure to the virus has been the main method of controlling the morbidity and mortality associated with hepatitis B. The first hepatitis B vaccine was manufactured by the purification and inactivation of hepatitis B surface antigen obtained from the plasma of chronic hepatitis B virus carriers.[1-3] This was soon followed by the production of hepatitis B surface antigen using recombinant DNA techniques and expression of the S component in yeast cells.[4]

All studies of the antibody response to currently licensed plasma derived hepatitis B vaccines and hepatitis B vaccines prepared by recombinant DNA technology have shown that between 5% and 10% or more of healthy immunocompetent subjects do not mount an antibody response to the surface antigen component present in these preparations (non-responders) or that they respond poorly (hyporesponders).[5-8]

The exact proportion depends partly on the definition of non-responsiveness or hyporesponsiveness, generally less than 10 IU/l or 100 IU/l respectively, against an international antibody standard.

Non-responders remain susceptible to infection with hepatitis B virus.[9] Several factors adversely affect the antibody response to hepatitis B surface antigen, including the site and route of injection, sex, advancing age, being overweight, immunosuppression, and immunodeficiency, but the mechanisms underlying non-responsiveness to the S component of hepatitis B surface antigen in humans remain largely unexplained. However, evidence is accumulating that different HLA-DR alleles are associated with specific low responsiveness in different ethnic populations. Considerable experimental evidence is available that the ability to produce antibody in response to specific protein antigens is controlled by dominant autosomal class II genes of the major histocompatibility complex in mice.[10-12] Much effort has been devoted to overcoming class II linked non-responsiveness to current hepatitis B vaccine.[13-15]

The pre-S1 and pre-S2 domains have an important immunogenic role in augmenting hepatitis B surface antibody responses, preventing the attachment of the

Academic Unit of Travel Medicine and Vaccines, Royal Free Hospital School of Medicine, London NW3 2PF
Jane N Zuckerman, *head*
Department of Primary Care and Population Sciences, Royal Free Hospital School of Medicine, London NW3 2PF
Caroline Sabin, *lecturer in medical statistics and epidemiology*
Medeva Scientific and Regulatory Affairs, Evans House, Regent Park, Leatherhead, Surrey KT22 7PQ
Fiona M Craig, *project manager*
A Williams, *director of clinical development*
WHO Collaborating Centre for Reference and Research on Viral Diseases, Royal Free Hospital School of Medicine, London NW3 2PF
Arie J Zuckerman, *professor of medical microbiology*
Correspondence to: Dr J N Zuckerman.

BMJ 1997;314:329–33

virus to hepatocytes and eliciting antibodies that are effective in clearing viruses, stimulating cellular immune responses, and circumventing genetic non-responsiveness to the S antigen.[14-18] Thus several studies indicate that pre-S components should be included in new recombinant or synthetic vaccines. For example, the pre-S2 region is more immunogenic in T and B cells than are the S regions in mice,[13 19] as is the case with pre-S1 in mice[14] and humans,[20] and circumvents S region non-responsiveness to antibody production.

Indeed, Milich *et al* showed that in mice the independent genetic regulation of immune responses to pre-S1, pre-S2, and S regions of hepatitis B surface antigen that are linked to the major histocompatibility complex would assure fewer genetic non-responders to a vaccine containing all three antigenic regions. Studies in humans of experimental recombinant hepatitis B vaccines containing all three S components of the viral envelope polypeptides showed enhanced immunogenicity of such preparations compared with conventional yeast derived vaccines.[21-23] We investigated the immunogenicity of a new hepatitis B vaccine containing the three antigenic components of both surface antigen subtypes *adw* and *ayw* in a group of healthcare staff who persistently showed no response to the conventional vaccine.

Subjects and methods

Vaccine

The vaccine used was manufactured by Evans Medical, a subsidiary of Medeva (Leatherhead, Surrey). The vaccine is a third generation vaccine containing pre-S1, pre-S2, and S antigenic components of both viral surface antigen subtypes *adw* and *ayw*. All three antigenic components are produced in a continuous mammalian cell line, the mouse c127 clonal cell line, after transfection of the cells with recombinant hepatitis B surface antigen DNA.[24 25] The vaccine was presented as an aluminium hydroxide adjuvant preparation of purified antigenic proteins in 1.0 ml of isotonic saline.

Study design

The study was a single centre, randomised, double blind dose-response study using four doses (5, 10, 20, and 40 μg) of the vaccine. Subjects were allocated randomly to receive in a double blind manner one of the four antigen doses. The same antigen dose of vaccine was given on two occasions intramuscularly into the deltoid two months apart. The primary objectives were to assess the immunogenicity and reactogenicity of the four doses of the vaccine and the kinetics of the immune response. A secondary objective was to evaluate the hepatitis B surface antibody response to vaccination. Non-seroconversion was defined as the presence of <10 IU/l hepatitis B surface antibody.

The sample size calculation assumed a 5% placebo response, although such a response was considered to be unlikely. The calculated group sizes necessary to have 90% power to detect a 45% response in the active groups ($P<0.05$; two tailed) gave group sizes of 23, which were made up to 28 to allow for up to five subjects dropping out in each treatment group.

Before inclusion each subject was screened for the presence of hepatitis B core and surface antibodies, and haematological and biochemical profiles were measured; women of childbearing age had a pregnancy test. Subjects were excluded if they were seropositive for hepatitis B core antibodies or had abnormal results in liver function tests. Fourteen days after the first visit each subject was then randomly allocated by a double blind method to receive one of the four antigen doses of the vaccine; 25 subjects were included in each dose group. Owing to minor discrepancies between the hepatitis B antibody titres obtained specifically at screening for this study and those previously documented in subjects' study files at the Royal Free Hospital School of Medicine both an intention to treat and per protocol population arose.

The intention to treat population included all randomised subjects who received the first vaccination at their second visit. The per protocol population consisted of the patients in the intention to treat population who did not violate any of the specified exclusion criteria. The analysis reported in this paper is based on the intention to treat population. However, when the analysis was repeated on the per protocol population the conclusions were essentially unchanged.

A standard physical examination was carried out on screening and at two and six months after the initial dose. Serum was collected for antibody evaluation at these times. The proportions of people who seroconverted and who were seroprotected at six months were considered to be primary end points. Geometric mean titres of hepatitis B surface antibody at both time points and seroconversion and seroprotection rates at two months were considered to be secondary end points.

Every subject was observed for 15 minutes after each vaccination, and any local or systemic reactions were recorded. Side effects and body temperatures were recorded on diary cards on the day of vaccination and for three days thereafter. Symptoms were divided into local, general, or other and were graded according to severity.

Serological methods

The seroconversion rate and geometric mean titres were measured to evaluate the immunogenicity in each group for all time points at which blood samples were taken.

Seroconversion was defined as the presence of hepatitis B surface antibody titres >10 IU/l while hepatitis B surface antibody titres of >100 IU/l were considered to be seroprotective. The serological hepatitis B surface antibody titrations using an international standard were carried out at the Royal Free Hospital School of Medicine using a commercial kit (Bioelisa, Biokit, Barcelona, Spain). The cut off point was in the range of 0-10 IU/l. Only subjects below 10 IU/l on the basis of this test were considered to be non-responders and were enrolled in the study.

The hepatitis B surface antibody titrations were repeated at the end of the study on all the serum samples which were maintained frozen at -20°C using another commercially available test kit (Ausab, Abbott Laboratories, North Chicago, USA).

Statistical analysis

The proportions of subjects seroconverting and protected at two and six months in each dose group were studied by logistic regression. Odds ratios and

95% confidence intervals are presented for the effect of a doubling in the dose of vaccine given—that is, an increase from 5 to 10 μg and from 10 to 20 μg, etc. Serological responses among the four dose groups, allowing for the presence of a trend in the response according to the dose of vaccine given, were further compared by linear regression with logarithmically transformed data. Geometric mean titres with confidence intervals for each dose group are presented. Because of the wide variation in the within individual differences in titres between months 2 and 6, the sign rank test was used to assess whether there was any overall change in titres after the booster dose.

Results

One hundred subjects were entered into the study, 25 in each of the four antigen dose groups. At screening, 14 subjects had hepatitis B surface antibody titres of >10 IU/l and were not included in the per protocol population. Of the 86 per protocol subjects, 22, 23, 20, and 21 subjects were entered into the four antigen dose groups respectively. All 100 subjects completed the study and received two doses of the vaccine.

The median age at entry was 38 years, and the median number of immunisations each subject had received of commercially available hepatitis B vaccines containing the S component was 5. There were no significant differences in age or sex distribution within the four antigen dose groups. Table 1 summarises the demographic details of the volunteers.

Reactogenicity

Fifteen per cent of subjects in each dose group experienced a reaction after their first vaccination. Overall, after each vaccination the incidence of local symptoms was higher than that of general symptoms. Most local symptoms were classed as either mild or moderate in severity, with only 11 severe events—predominantly pain at the site of injection—being reported for the 200 doses of vaccine. The incidence of these across the four antigen dose groups was 2, 4, 3, and 2 respectively.

General symptoms, including chills, dizziness, headache, nausea, and diarrhoea, occurred within 24 hours of immunisation and were transient. No serious adverse events occurred during the study and no dose related incidence was seen for either local or general symptoms.

Immunogenicity

Two months after a single dose of vaccine 69 subjects seroconverted with a hepatitis B surface antibody titre of >10 IU/l. The seroconversion rates for each of the four antigen dose groups ranged from 52% to 84% in the four dose groups (table 2). The overall rate of seroconversion four months after the booster dose was 70%. Seroconversion rates in the four dose groups were 60%, 76%, 64%, and 80% respectively.

Although a significant dose-response effect on seroconversion rates was seen at two months ($P=0.03$) with a 56% increase in the seroconversion rate for each doubling in the dose of vaccine given, by six months this effect had become non-significant ($P=0.24$). However, the confidence interval for the odds ratio was wide and the upper limit of the confidence interval suggested that an odds ratio as high as 1.86 could be consistent with the trial results.

Table 1 Demographic details of subjects in trial (intention to treat analysis)

Antigen (μg)	5	10	20	40
Mean (SD) age (years)	36 (12.0)	39 (11.5)	37 (11.8)	40 (11.9)
No of men/women	8/17	15/10	15/10	12/13
Mean weight (SD) (kg)	72.0 (15.5)	74.6 (13.0)	77.0 (14.8)	76.0 (14.7)
Median No of previous inoculations	5	5	5	6
Ethnic group:				
White	23	23	23	23
Black		1	1	1
Chinese	1	1		
Asian	1		1	1

Table 2 Numbers (percentages) of subjects who seroconverted two and six months after vaccination (intention to treat analysis)

Antigen (μg)	No of subjects	Month 2	Month 6
5	25	13 (52)	15 (60)
10	25	18 (72)	19 (76)
20	25	17 (68)	16 (64)
40	25	21 (84)	20 (80)
Total	100	69 (69)	70 (70)
Odds ratio for doubling in dose of vaccine (95% confidence interval)		1.56 (1.05 to 2.33)	1.26 (0.85 to 1.86)
P value		0.03	0.24

Table 3 Numbers (percentages) of subjects who were seroprotected at two and six months after vaccination (intention to treat analysis)

Antigen (μg)	No of subjects	Month 2	Month 6
5	25	5 (20)	1 (4)
10	25	3 (12)	6 (24)
20	25	8 (32)	10 (40)
40	25	11 (44)	9 (36)
Total	100	27 (27)	26 (26)
Odds ratio for a doubling in dose of vaccine (95% confidence interval)		1.63 (1.07 to 2.49)	1.87 (1.20 to 2.92)
P value		0.02	0.006

The overall rate of arbitrary seroprotection, defined as the presence of hepatitis B surface antibody titres of >100 IU/l, was 27% (27/100) after the first immunisation and 26% (26/100) after the booster. At two months seroprotection rates ranged from 12% to 44% in the four dose groups. At six months they were 4%, 24%, 40%, and 36% respectively (table 3). There was a significant trend with dose at both two and six months ($P=0.02$ and 0.006 respectively), although it seems that the booster dose may be less effective in achieving a sustained serological response, as several subjects who were protected at two months had lost their protection by six months.

There was a significant dose-response effect on geometric mean titre levels at two months ($P=0.002$) (table 4). Administration of a booster dose of the vaccine at two months did not produce a corresponding rise in geometric mean titres within any of the antigen dose groups. Within subjects, variation was wide in the change in titres between the two visits, with changes ranging from a drop of 16 800 IU/l to an increase of 6600 IU/l in two subjects with initially high titres. However, the median change was zero and there was no systematic pattern to the changes ($P=0.19$, sign rank test). Despite this, the strong dose-response effect remained at six months ($P=0.009$) (table 4).

Table 4 Geometric mean titres (IU/l) (with 95% confidence intervals) at two and six months after vaccination (intention to treat analysis)

		Month	
Antigen (μg)	No of subjects	2	6
5	25	10.0 (3.8 to 26.7)	11.9 (5.7 to 25.1)
10	25	26.9 (13.1 to 55.3)	28.6 (12.0 to 68.1)
20	25	58.5 (17.1 to 200.2)	57.5 (16.8 to 197.0)
40	25	79.7 (27.5 to 230.5)	61.8 (23.1 to 165.5)
Total	100	33.5 (20.2 to 55.6)	33.2 (20.6 to 53.6)
P value for trend		0.002	0.009

There were no significant differences in the hepatitis B surface antibody titres obtained by the two different assay systems used.

Discussion

Factors affecting the immune response

Inactivated hepatitis B vaccines have been available since 1981; they are derived from plasma or from yeast recombinant DNA. These vaccines have been shown to be both immunogenic and safe, but 5-10% of healthy people do not respond to them [6-8 26] and variants of hepatitis B virus that are not neutralised by vaccine induced hepatitis B surface antibody have recently emerged. Several factors play a part in the failure to mount an antibody response to hepatitis B surface antigen. These include the site of injection, the deltoid area being preferred to the buttocks as fat lacks antigen presenting cells, resulting in a delay in presentation of antigen to T and B cells[27]; increasing age; sex; smoking; being overweight; immunosuppression; and immunogenetic makeup. However, after the identification of an immunodominant domain in the pre-S2 region of hepatitis B surface antigen[28] and the observation that immunologically non-responsive mice developed antibodies corresponding to the pre-S epitope, vaccines have been prepared containing all three antigenic components—pre-S1, pre-S2, and S.

Guidelines for immunisation

The recommendations for immunisation against hepatitis B are well known, and healthcare workers are at occupational risk of exposure to hepatitis B virus. A proportion are non-responders and remain susceptible to infection. Recent guidelines from the United Kingdom Department of Health on the immunisation of healthcare workers has led to improvements in immunisation programmes and consequently uptake of hepatitis B vaccine.[29] In this study we evaluated the immunogenicity and reactogenicity of a new vaccine in healthcare workers who had previously failed to develop an immune response after multiple doses of currently available hepatitis B vaccines. The new vaccine preparation produced a response in a group of persistent non-responders, with an overall seroconversion rate of 69% after a single dose, and a significant dose-response effect was seen. After a further four months, however, there was no significant dose effect on the proportion of subjects who seroconverted—that is, hepatitis B surface antibody titre >10 IU/l in the four antigen dose groups. This suggests that it may be as effective to use a single dose of either 20 μg or 40 μg than two doses of, say, 10 μg or 20 μg. Although the dose-response effect six months later was not significant, seroconversion rates were highest in the group receiving the highest dose of vaccine (80%), and the confidence interval for the odds ratio suggests that we cannot rule out the possibility of an important dose-response effect. This was a phase II clinical trial and as such, several questions remain to be answered concerning the precise schedule of vaccination and the groups for whom it would be advocated. Phase III comparative clinical trials are currently being undertaken.

Seroprotection and seroconvertion rates

Although the aim of this study was to determine the immunogenicity of this vaccine in non-responders, 14 subjects included in the intention to treat population had a hepatitis B surface antibody titre on screening of >10 IU/l but <100 IU/l. Thus, the seroconversion rates quoted may be higher than expected. However, when the analysis was repeated including only the per-protocol population, seroconversion rates were only slightly lower (64% and 66% at two months and six months respectively), and the conclusions remained unchanged.

A few subjects (16% (5/31)) whose antibody titre remained below 10 IU/l after one dose of the vaccine did seroconvert after the booster dose. We could not determine the cause of this delayed immune response. An unexpected observation was that the administration of a booster dose did not significantly enhance the immune response in the patients overall. However, there was wide individual variability both in the titres at two and six months and in the change in titres after the booster dose.

No empirical data are available for the hepatitis B surface antibody titre required for protection against particular routes of infection or the size of the infectious inoculum. The minimal protective titre has been assumed almost universally to be 10 IU/l, and immunological memory is thought to ensure protection even after circulating antibody becomes undetectable.[3 5 29-32] In the United Kingdom 100 IU/l is regarded as the desired antibody titre for complete seroprotection after immunisation of normal healthy subjects. Nevertheless, the need for booster inoculation after decay in antibody titres is still the subject of debate internationally.

The results of this trial have been based on the measurements of hepatitis B surface antibody titres but the pre-S1 and pre-S2 antibody response was not measured. Further analysis of the pre-S1 and pre-S2

Key messages

- Up to 15% of healthy people do not respond to currently licensed hepatitis B vaccines
- Incorporation of the pre-S1 and pre-S2 components with the S antigen overcame this non-response in 69% of healthcare workers with a history of persistent non-response to conventional hepatitis B vaccines
- Significantly higher geometric mean titre levels were obtained with increased dosage of vaccine
- A single dose of 20 μg of the new vaccine seems to be effective in terms of seroconversion, seroprotection, and geometric mean titres

antibody response will be undertaken when reproducible assays become available and have been validated.

A proportion of subjects (34% (30/86)) did not mount a hepatitis B surface antibody response after two doses of the vaccine. These subjects will receive a further dose of the vaccine and be followed up. Studies were also undertaken to investigate the relation between the humoral response to hepatitis B vaccine and immunogenetic profiles in this population group, the results of which have been submitted for publication.

We thank the doctors and others who referred non-responders to us, and the volunteers, without whom this study could not have been undertaken. The laboratory tests were carried out by the staff of the department of virology and the WHO Collaborating Centre for Reference and Research on Viral Diseases at the Royal Free Hospital and School of Medicine.

Funding: The study was supported by research grants available to the Academic Unit of Travel Medicine and Vaccines, the WHO Collaborating Centre for Reference and Research on Viral Diseases, the Violet Richards Charitable Trust; study costs were paid for by Medeva.

Conflict of interest: None.

1 Szmuness W, Stevens CE, Zang EA, Harley EJ, Kellner A. A controlled clinical trial of the efficacy of the hepatitis B vaccine (Heptavax B). A Final Report. *Hepatology* 1981;1:377-85.
2 Hadler SC, Frances DP, Maynard JE, Judson FN, Thompson SE, Echenberg DF. Long-term immunogenicity and efficacy of hepatitis B vaccine in homosexual men. *N Engl J Med* 1986;315:209-14.
3 Jilg W, Schmidt M, Deinhardt F. Immune response to hepatitis B revaccination. *J Med Virol* 1988;24:377-84.
4 Jilg W, Schmidt M, Zoulek G, Lorbeer B, Wilkse B, Deinhardt F. Clinical evaluation of a recombinant hepatitis vaccine. *Lancet* 1984;11:1174-5.
5 Westmoreland D, Player V, Heap DC, Hammond A. Immunization against hepatitis B--what can we expect? *Epidemiol Infect* 1990;104:499-509.
6 Dienstag JL, Werner BG, Polk BF, Snydman DR, Craven DE, Platt R. Hepatitis B vaccine in health care personnel: safety, immunogenicity, and indicators of efficacy. *Ann Intern Med* 1984;101:34-40.
7 Craven DE, Awdeh ZL, Kunches LM, Yunis EJ, Dienstag JL, Werner BG. Non-responsiveness to hepatitis B vaccine in health care workers. *Ann Intern Med* 1986;105:356-60.
8 Wood RC, MacDonald KL, White KE, Hedberg CW, Hanson M, Osterholm MT. Risk factors for lack of detectable antibody response following hepatitis B vaccination of Minnesota health care workers. *JAMA* 1993;270:2935-9.
9 Boag F. Hepatitis B: heterosexual transmission and vaccination strategies. *Int J STD and AIDS* 1991;2:318-24.
10 Milich DR. Immune response to hepatitis B virus protein relevance of the murine model. *Seminars in Liver Disease* 1991;11:93-112.
11 Alper CA, Kruskall MS, Marcus-Bagley D, Craven DE, Katz AJ, Brink SJ. Genetic prediction of nonresponse to hepatitis B vaccine. *N Engl J Med* 1989;321:708-12.
12 Kruskall MS, Alper CA, Awdeh Z, Yunis EJ, Marcus-Bagley D. The immune response to hepatitis B vaccine in humans: inheritance patterns in families. *J Exp Med* 1992;175:495-502.
13 Milich DR, McNamara NK, McLachlan A, Thornton GB, Chisari FV. Distinct H-2 linked regulation of T-cell responses to the pre-S and S regions of the same hepatitis B surface polypeptide allows circumvention of non-responsiveness to the S region. *Proc Natl Acad Sci USA* 1985;82:8168-72.
14 Milich DR, McLachlan A, Chisari FV, Kent SB, Thornton GB. Immune response to the pre-S(1) region of hepatitis B surface antigen (HBsAg): a pre-S(1)-specific T cell response can bypass nonresponsiveness to the pre-S(2) and S regions of the HBsAg. *J Immunol* 1986;137:315-22.
15 Arif M, Mitchison NA, Zuckerman AJ. Genetics of nonresponders to hepatitis B surface antigen and possible ways of circumventing "nonresponse". In: Zuckerman AJ, ed. *Viral hepatitis and liver disease.* New York: Liss, 1988:714-6.
16 Gerlich W, Deepen R, Heerman KH, Krone B, Lu XY, Seifer M. Protective potential of hepatitis B virus antigens other then the S gene protein. *Vaccine* 1990;8:563-8.
17 Klinkert M, Theilmann L, Pfaff E, Schaller H. Pre-S antigens and antibodies early in the course of acute hepatitis B virus infection. *J Virol* 1986;58:522-5.
18 Alberti A, Pontisso P, Tagariello GF, Belussi F. Antibody response to pre-S2 and hepatitis B virus induced liver damage. *Lancet* 1988; i:1421-4.
19 Milich DR, Thornton GB, Neurath AR, Kent SB, Michel M-L, Tiollais P. Enhanced antigen. *Science* 1985;228:1195-9.
20 Ferrari C, Penna A, Bertoletti A, Cavalli A, Valli A, Schianchi C, *et al.* The pre-S1 antigen of hepatitis B virus is highly immunogenic at the T cell level in man. *J Clin Invest* 1989;84:1314-9.
21 Yap I, Guan R, Chan SH. Recombinant DNA hepatitis B vaccine containing pre-S components of the HBV coat protein—a preliminary study on immunogenicity. *Vaccine* 1992;10:439-42.
22 Shouval D, Ilan Y, Adler R, Deepan R, Panet A, Even-Chen Z. Improved immunogenicity in mice of a mammalian cell-derived recombinant hepatitis B vaccine containing pre-S1 and pre-S2 antigens as compared with conventional yeast-derived vaccines. *Vaccine* 1994;12:1453-9.
23 Yap I, Guan R, Chan SH. Study on the comparative immunogenicity of a recombinant DNA hepatitis B vaccine containing pre-S components of the HBV coat protein with non pre-S containing vaccines. *J Gastroenterol Hepatol* 1995;10:51-5.
24 Yoneyama T, Akatsuka T, Miyamura T. Stable expression of the hepatitis B virus surface antigen containing pre-S2 protein in mouse cells using a bovine papillomavirus vector. *J Gen Virol* 1988;69:1931-9.
25 Samanta H, Youn BW. Expression of hepatitis B virus surface antigen containing the pre-S region in mammalian cell culture system. *Vaccine* 1989;7:69-76.
26 Eddleston A. Modem vaccines: hepatitis. *Lancet* 1990;335:1142-4.
27 Zuckerman JN, Cockcroft A, Zuckerman AJ. Site of injection for vaccination. *BMJ* 1992;305:1158.
28 Neurath AR, Kent SBH, Strick N. Location and chemical synthesis of a pre-S gene coded immunodominant epitope of hepatitis B virus. *Science* 1984;224:392-5.
29 BMA. *A code of practice for implementation of the UK hepatitis B immunisation guidelines for the protection of patients and staff.* London: BMA, 1995.
30 Legler K, Strohmeyer H, Ritter S, Gerlich WH, Thomssen R. Kinetics, subtype specificity and immunoglobulin class of anti-HBs induced by hepatitis B vaccine. *Develop Biol Standard* 1983;54:179-89.
31 Prince AM, Brotman B, Purcell RF, Gerin JL. A final report on safety and immunisation of a bivalent aqueous subunit HBV vaccine. *J Med Virol* 1984;15:399-419.
32 Prince AM. Revaccination against hepatitis B. *Lancet* 1991;ii:61.

(Accepted 15 November 1996)

A BASIC LESSON RELEARNT

The singing histopathologist

David was not a frequent attender at surgery on his own behalf. With his marching gait and handlebar moustache, I would see him striding around the practice area dispensing Royal British Legion aid and support to my patients. One day, however, he came to tell me that he was dying. He demonstrated his jaundice with a wry smile and then proffered the diagnosis—cancer of the bile duct. "It runs in my family, my father died of it," he said sadly. I could not disagree that he was profoundly jaundiced but tried to reassure him that it was more likely to be something simple and probably less rare.

Liver function tests showed a depressingly obstructive picture. David began to lose weight. An ultrasound showed obstruction at the porta hepatis with an ill defined mass which was probably a cholangiocarcinoma. At the local hospital a technically difficult endoscopic retrograde cholangiopancreatographic examination was carried out which showed multiple strictures in the biliary system. Computed tomography provided no further information. It looked as though the patient was right. David remained resigned to his future and began to sort out his affairs.

I could not but agree with the opinion of the consultants from the major teaching hospital. David clearly had malignant disease, and it seemed that nothing further could be done. I sought the advice of my gastroenterologist father, who worked at another university hospital. Our views coincided that tumour removal might have a part to play. He kindly accepted this rather circuitous referral and agreed to assess David for hepatectomy and liver transplantation. David was worked up, fattened up, and a donor liver was found. He was opened up. The abdomen contained a substantial amount of tumour. It extended outside the liver, infiltrating the omentum and the diaphragm. A transplant was both technically impossible and unlikely to achieve a cure. Further exploration showed that local excision or a surgical bypass were also impossible. He was sewn up and returned to the ward. Although his symptoms were alleviated by a percutaneous stent, he had to be told bad news—again.

Seven years later he is alive and well after successful chemotherapy for the B cell non-Hodgkin's lymphoma found on the biopsy taken by the surgeon at laparotomy. No tumour can be accurately characterised before it is viewed down a microscope. The show is not over until the histopathologist sings.

Ian Neale *is a general practitioner in Oxfordshire*

Meta-analysis of trials of prophylactic antibiotics for children with measles: inadequate evidence

Frank Shann

See editorial by Potter and Hussey

Intensive Care Unit, Royal Children's Hospital, Parkville, Victoria 3052, Australia
Frank Shann, *professor of critical care medicine*

BMJ 1997;314:334–7

Abstract

Objective: To assess whether antibiotics should be given to all children with measles in communities with a high case fatality rate.
Design: Meta-analysis of randomised controlled trials that compared routine antibiotic prophylaxis with no antibiotic treatment or selective treatment of pneumonia or sepsis.
Subjects: Six trials of children admitted to hospital with measles: five in Glasgow, London, or New York between 1939 and 1954; and one in India in 1967.
Main outcome measures: Incidence of pneumonia or sepsis, and mortality.
Results: All but one of the trials were unblinded, and randomisation was either not described or was by alternate allocation. In four studies, the incidence of pneumonia or sepsis in the control group was similar to that in the antibiotic prophylaxis group; in the other two studies, the incidence of pneumonia or sepsis was unusually high in the control group so these children had a higher complication rate than the antibiotic group. Four of the 764 children given antibiotics died compared with one of the 637 controls (exact odds ratio 4.0, mid-P corrected 95% confidence interval 0.5 to 101.6).
Conclusion: The quality of the trials reviewed was poor, and they provide weak evidence for giving antibiotics to all children with measles. Available evidence suggests that, when mortality from measles is high, all children with measles should be treated with vitamin A but antibiotics should be given only if a child has clinical signs of pneumonia or other evidence of sepsis.

Introduction

Measles causes more than a million deaths a year, and most of these deaths are from pneumonia in children less than 5 years old.[1] There is evidence that pneumonia in children with measles is often caused by bacterial infection. Histological features of bacterial pneumonia were found at necropsy in nine of 26 children in Uganda,[2] and five of 21 children in South Africa.[3] Bacteria were isolated from lung aspirates in 71 of 75 children studied in London in 1931[4] and, in more recent studies, from 15 of 22 children in South Africa,[5] two of 21 children in Colombia,[6] and 20 of 56 children in Nigeria.[7] In adults with measles and pneumonia in the United States, bacteria were isolated from transtracheal aspirate in 10 of 16 patients in one study[8] and 35 of 106 patients in another.[9]

The evidence that pneumonia in children with measles is often caused by bacteria suggests that, in countries where there is a high case mortality, it might be sensible to give antibiotics to all children with measles. However, there has been no systematic evaluation of the evidence for such a policy, and there is good evidence that routine antibiotic prophylaxis does not prevent pneumonia developing in children with upper respiratory tract infections caused by other viruses.[10] To assess the strength of the evidence for giving prophylactic antibiotics to all children with measles, I performed a meta-analysis of randomised controlled trials in which routine antibiotic prophylaxis was compared with no treatment or selective treatment for pneumonia or sepsis.

Methods

I performed a Medline search for the years 1966-95, searching on measles plus either antibiotics, penicillins, sulphonamides, prospective studies, or randomised controlled trials. I also used the results of my previous study of pneumonia in children which included a hand search of every journal in the University of Melbourne medical library for the period 1935-46 inclusive.[11]

For each study, I sought information about the selection of patients; randomisation procedures; exclusions after randomisation; and the number of patients randomised, the number who developed pneumonia or sepsis, and the number who died. In my analyses of the development of pneumonia or sepsis and of mortality nearly half the cells contained five or fewer items, so I performed the meta-analyses with StatXact.[12]

Results

Studies

I identified six randomised controlled trials of the use of prophylactic antibiotics in children with measles (table 1).[13-18] Five of the trials were conducted in Glasgow, London, or New York between 1939 and 1954,[13-17] a time when measles was often complicated by bronchopneumonia but controlled trials were not well designed; the sixth study was conducted in India in the 1960s.[18] Apart from two studies in which the method of randomisation was not specified,[15 18] alternate children were allocated to either an antibiotic or a control group when they were admitted to the trial; in four studies antibiotics were given to all children who had pneumonia at the time of admission and to any child in the control group who developed pneumonia or sepsis,[15-18] and the other two studies did not give any antibiotics to children in the control group.[13 14] All but one of the studies were unblinded,[13-17] and only one paper mentioned withdrawals from the trial.[13] None of the papers provided information about antibiotic treatment given before randomisation.

Three published studies were excluded from this analysis because they were not randomised.[19-21] Thompson reported that bronchopneumonia developed in 1.7% of 352 children treated with an antibiotic, and in 4.8% of 762 controls.[19] On the other hand, Weinstein found pneumonia at the time of

Table 1 Details of controlled randomised trials included in meta-analysis of antibiotic prophylaxis for children with measles

Trial	Patients	Randomisation	Controls	Pneumonia: Definition	Pneumonia: Diagnosis blinded	Baseline comparisons	Withdrawals	Antibiotic
Anderson 1939[13]	Consecutive inpatients 86% aged <6 years	Alternate patients	No placebo No antibiotic	No	No	Age, sex, duration of illness, complications	1 (did not have measles)	Sulphanilamide
Hogarth 1939[14]	Consecutive inpatients 74% aged <4 years	Alternate patients with "same degree of severity"	No placebo No antibiotic	Clinical or *x* ray	No	Severity of disease, age	None?	Sulphanilamide derivative
Gibel *et al* 1942[15]	Consecutive inpatients All aged <6 years	"Divided on admission into two groups"	No placebo Antibiotic for pneumonia or sepsis*	No	No	Age, sex, duration of illness	None?	Sulphathiazole
Karelitz *et al* 1951[16]	Consecutive inpatients All aged <9 years	First 15 given antibiotic, then alternate patients	No placebo Antibiotics for pneumonia or sepsis	No	No	Age	None?	Chlortetracycline, procaine penicillin
Karelitz *et al* 1954[17]	Consecutive inpatients 98% aged <10 years	Alternate patients	No placebo Antibiotic for pneumonia or sepsis	Clinical or *x* ray	No	Age, duration of rash	None?	Benzathine or procaine penicillin
Prasad *et al* 1967[18]	Inpatients and outpatients 90% aged <5 years	"Divided into two subgroups"	Placebo Antibiotic for pneumonia	*x* ray	Not specified	None	None?	Tetracycline

*No controls developed pneumonia or sepsis in this study.

admission to hospital in 21.5% of 130 children who had been treated with an antibiotic, and 8.1% of 298 children who had not had an antibiotic.[20] In Senegal the case mortality from measles fell substantially after an increase in measles immunisation and administration of co-trimoxazole to all children less than 3 years old who had measles[21]; however, immunisation has been shown to reduce the case mortality from measles,[22 23] and the co-trimoxazole may have had little or no effect.

Development of pneumonia or sepsis

In my analysis of the development of pneumonia or sepsis after admission (table 2), the exact test for homogeneity showed that there was no common odds ratio across the six 2×2 tables ($P < 0.00005$), so I did not report the odds ratio. The scanty details provided in the papers and the small sample sizes meant that the cause of the lack of homogeneity could not be determined. It was possible to reject the null hypothesis that all the 2×2 tables in table 2 had an odds ratio of 1.0 (exact two sided test $P = 0.0004$); however, the P value was 0.833 when the two studies with an unusually high mortality in the control group[17 18] were removed.

In the first four studies[13-16] the incidence of pneumonia or sepsis in the control group was similar to that in the antibiotic prophylaxis group (11/462 (2%) *v* 12/447 (3%)); in the other two studies,[17 18] where there was an unusually high incidence of pneumonia or sepsis in the control group, there were more complications in the control group than in the antibiotic group (23/161 (14%) *v* 2/234 (1%)).

Table 2 Number (percentage) of children developing pneumonia or sepsis in randomised controlled trials included in meta-analysis of antibiotic prophylaxis for children with measles

Trial	Antibiotic prophylaxis	Control
Anderson 1939[13]	4/46 (9)*	3/48 (6)*
Hogarth 1939[14]	2/159 (1)	5/170 (3)
Gibel *et al* 1942[15]	6/153 (4)*	0/201
Karelitz *et al* 1951[16]	0/89	3/43 (7)
Karelitz *et al* 1954[17]	2/156 (1)*	12/81 (15)
Prasad *et al* 1967[18]	0/78	11/80 (14)

*Excluding children with pneumonia or sepsis at time of admission.

Table 3 Number (percentage) of children who died in randomised controlled trials included in meta-analysis of antibiotic prophylaxis for children with measles

Trial	Antibiotic prophylaxis	Control
Anderson 1939[13]	3/63 (5)*	1/62 (2)*
Hogarth 1939[14]	0/159	0/170
Gibel *et al* 1942[15]	1/200 (1)	0/201
Karelitz *et al* 1951[16]	0/89	0/43
Karelitz *et al* 1954[17]	0/175	0/81
Prasad *et al* 1967[18]	0/78	0/80

*Including children with pneumonia or sepsis at time of admission.

Mortality

There were four deaths in the 764 children given prophylactic antibiotics, and only one in the 637 children in the control group (table 3). The exact test for homogeneity gave a P value of 1.00, and the exact common odds ratio was 4.0 (mid-P corrected 95% confidence interval 0.5 to 101.6). There is, therefore, no evidence that mortality was lower when antibiotics were given routinely rather than selectively or not at all.

Discussion

The main limitations of this analysis were that the six controlled trials included a total of only 1304 children and all six trials were poorly designed—randomisation was not described or was by alternate allocation, all but one were unblinded, and little information was provided about withdrawals. Only one of the trials[13] had a mortality of 1% or more, although two others[14 15] were in communities where the mortality had been more than 1% in the immediately preceding years, when antibiotics were not available.

Because of the poor quality of these studies , any inferences must be tentative. The studies suggest that routine antibiotic treatment might reduce the risk of developing pneumonia or sepsis ($P = 0.0004$), but the effect was small and disappeared when the two studies

with unusually high complication rates in the control group were excluded (table 2). These findings are consistent with the evidence that routine antibiotic treatment of non-measles upper respiratory tract infection does not prevent pneumonia.[10]

The studies reviewed here provide no evidence that routine antibiotic treatment resulted in a lower mortality (four deaths in 764 children) than no antibiotic treatment (one death in 232 children) or selective treatment when complications developed (no deaths in 405 children) (table 3). However, the small number of deaths means that the possibility of a reduced mortality from routine prophylaxis cannot be excluded. Some of the children who died may have already had pneumonia or sepsis at the time they were admitted to the trials. Antibiotic treatment of cases with pneumonia or sepsis seemed to have a considerable effect on mortality: for example, at the Kingston Avenue Hospital, New York, 2.63% of 3611 children with measles died in 1935-40, before antibiotics were used, compared with only 0.74% of 1213 children in 1941, when sulfathiazole was first used.[15]

Key messages

- Since many deaths from measles in young children are caused by bacterial pneumonia it might be sensible to give antibiotics to all children with measles where there is high case mortality, but there has been no systematic evaluation of such a policy
- Six randomised controlled trials of prophylactic antibiotics in children with measles were found
- All trials were poorly designed and preceded the introduction of vitamin A for measles
- Prophylactic antibiotics had little or no effect on mortality from measles
- In communities with mortality from measles of 1% or more, all children with measles should be treated with vitamin A but antibiotics should be given only if a child has clinical signs of pneumonia or sepsis

Recommendations

Mortality from measles is said to be high if it is 1% or more.[24] How should children with measles be managed in communities with a high mortality? All such children should be treated with high doses of vitamin A, which substantially reduces mortality from measles.[24 25] Children who have clinical signs of pneumonia (cyanosis, inability to feed, chest indrawing, or tachypnoea) or other evidence of sepsis should be given antibiotics,[26] but should antibiotics be given to children with measles who have no clinical signs of pneumonia or sepsis? The controlled trials of prophylactic antibiotics for measles provide only weak evidence that they reduce the incidence of pneumonia and no evidence that they reduce mortality. In addition, the trials were performed before the introduction of vitamin A treatment for measles and before the development of detailed guidelines for the early diagnosis of pneumonia in children. The routine administration of prophylactic antibiotics to all children with measles would be expensive, and it would encourage the development of antibiotic resistance.

To prevent unnecessary admissions, conserve scarce resources and reduce cross infection, it is important that only high risk cases of measles are admitted to hospital in developing countries.[27] In these circumstances a high proportion of children admitted to hospital will have pneumonia or sepsis and will therefore need treatment with an antibiotic.

The poor quality of the trials reviewed here suggests a need for further studies. However, a controlled trial of routine antibiotic prophylaxis would need 3000 patients in each group to detect a halving in mortality from 2% to 1% with a two sided α error of 0.05 and a β error of 0.2, and it would be a major exercise to mount such a large study in a developing country. Given the pressing need for large controlled trials of vaccines and trials of the treatment of established pneumonia in the presence of antibiotic resistant organisms, a controlled trial of prophylactic antibiotics for measles has a low priority.

Funding: None.

Conflict of interest: None.

1 World Health Organisation. *The world health report 1995: bridging the gaps: report of the director-general.* Geneva: WHO, 1995.
2 De Buse PJ, Jones G, Nairdoo A. A comparison of penicillin and tetracycline in pulmonary complications of measles; a clinical and radiological assessment. *East Afr Med J* 1969;46:46-54.
3 Kaschula R, Druker J, Kipps A. Late morphologic consequences of measles: a lethal and debilitating lung disease among the poor. *Rev Infect Dis* 1983;5:395-404.
4 Ellison JB. Pneumonia in measles. *Arch Dis Child* 1931;6:37-51.
5 Wesley AG, Sutton JB, Widrich AJ. The aetiology of pneumonia associated with measles in Bantu children. *S Afr Med J* 1971;45:1402-4.
6 Dover A, Escobar JA, Duenas AL, Leal EC. Pneumonia associated with measles. *JAMA* 1975;234:612-4.
7 Morton R, Mee J. Measles pneumonia: lung puncture findings in 56 cases related to chest X-ray changes and clinical features. *Ann Trop Paediatr* 1986;6:41-5.
8 Olson RW, Hodges GR. Measles pneumonia. *JAMA* 1975;232:363-5.
9 Gremillion DH, Crawford GE. Measles pneumonia in young adults: an analysis of 106 cases. *Am J Med* 1981;71:539-42.
10 Gadomski AM. Potential interventions for preventing pneumonia among young children: lack of effect of antibiotic treatment for upper respiratory infections. *Pediatr Infect Dis J* 1993;12:115-20.
11 Shann F. Etiology of severe pneumonia in children in developing countries. *Pediatr Infect Dis* 1986;5:247-52.
12 StatXact-Turbo. Cambridge: Cytel Software Corporation, 1992.
13 Anderson T. Sulphanilamide in the treatment of measles. *BMJ* 1939;i: 716-8.
14 Hogarth JC. Para-benzylaminobenzenesulphonamide in the prevention of measles complications. *BMJ* 1939;i:718-20.
15 Gibel H, Litvak AM. Sulfathiazole in the treatment of measles and its complications. *J Pediatr* 1942;21:315-20.
16 Karelitz S, King H, Curtis B, Wechsel M. Use of Aureomycin and penicillin in the treatment of rubeola in the pre-eruptive and early eruptive phase. *Pediatrics* 1951;7:193-9.
17 Karelitz S, Chang C, Matthews ZE. The prophylaxis and treatment of bacterial complications of measles with benzethacil and aqueous procaine penicillin G. *J Pediatr* 1954;44:357-63.
18 Prasad R, Mathur GP, Trehan OP, Mehrotra, Dayal RS. A clinical and radiological study of measles. *Indian Pediatr* 1967;4:243-50.
19 Thompson AR, Greenfield CRM. Chemotherapy in measles and whooping-cough. prophylaxis and treatment of complications. *Lancet* 1938;i:991-4.
20 Weinstein L. Failure of chemotherapy to prevent the bacterial complications of measles. *N Engl J Med* 1955;253:679-83.
21 Samb B, Simondon F, Aaby P, Whittle H, Seck AMC. Prophylactic use of antibiotics and reduced case fatality in measles infection. *Pediatr Infect Dis J* 1995;14:695-6.
22 Aaby P. Assumptions and contradictions in measles and measles immunization: is measles good for something? *Soc Sci Med* 1995;41:673-86.
23 Lau Y, Chow C, Leung T. Changing epidemiology of measles in Hong Kong from 1961 to 1990—impact of a measles vaccination program. *J Infect Dis* 1992;165:1111-5.
24 Joint WHO/UNICEF statement. Vitamin A for measles. *Wkly Epidemiol Rec* 1987;19:133-4.
25 Hussey GD, Klein M. Routine high-dose vitamin A therapy for children hospitalized with measles. *J Trop Paediatr* 1993;39:342-5.
26 World Health Organisation. *Technical bases for the WHO recommendations on the management of pneumonia in children at first-level health facilities.* Geneva: WHO, 1991.
27 Forbes CE, Scheifele DW. The management of measles in Nairobi. *East Afr Med J* 1973;50:159-68.

(Accepted 15 November 1996)

Commentary: Summary statistics of poor quality studies must be treated cautiously

Jesse A Berlin

Apart from the lack of adherence to modern standards of trial design, a striking feature of the studies considered by Frank Shann is the extreme degree of heterogeneity of the findings. Shann argues that this combination of heterogeneity and low quality precludes the confident estimation of a summary measure of treatment effectiveness against development of pneumonia or sepsis. I will try to show that exploring sources of heterogeneity in situations such as this can provide clinical insights and generate hypotheses.

Unfortunately, given the uniformly suboptimal quality of the existing studies, we cannot examine quality of the studies as a source of heterogeneity. At the same time, its uniform poorness means that study quality is not likely to explain the heterogeneity of the findings. For illustrative purposes, however, suppose that we summarise separately the three studies with the highest risks of infection in the control groups. The exact stratified summary odds ratio for those studies is 0.04 (95% confidence interval 0.00 to 0.18), suggesting a substantial benefit from antibiotic prophylaxis when the baseline risk is high, with little evidence of heterogeneity between the studies (P = 1.00 for test of common odds ratio). The high rates of infection in the control groups of the three studies might be "real" and rooted in the epidemiological aspects of measles in the populations studied, or they might be due to chance.

These same three studies also happen to be the three most recently conducted studies. The colinearity of date of publication and baseline risk makes interpretation of the result for this subgroup somewhat ambiguous. This ambiguity stems from the possibility that other clinically relevant factors might have varied with time—for example, improvements in subtle aspects of study design or changes in the clinical characteristics of patients. Nevertheless, the stratification and summarisation, although not the optimal statistical approach in this situation,[1] have raised a clinical hypothesis that might not otherwise have been raised.

What are we to conclude from this exercise? We might conclude that antibiotic prophylaxis is effective, on the basis that an effect as large as the one observed is unlikely to have been produced either by chance or by bias. The danger with such an argument, and one reason not to summarise these studies, is that many readers will assign a high degree of validity to a quantitative summary of poor quality studies simply because it is quantitative and in spite of any caveats offered by the meta-analyst. My view is that the combined odds ratio is simply a summary from which we can learn about the data. Without more studies of higher quality we are unlikely to solve our dilemma.

Thus, one message from the above, and from Shann's paper, is that the decision about whether to calculate a quantitative summary of the data is not always straightforward, and different investigators could legitimately arrive at different decisions. From a clinical perspective, the above summaries may not, in fact, tell the whole story. In the same three studies that showed large reductions in infection rates, there were no deaths. Overall, there was no evidence of a reduction in mortality associated with antibiotic prophylaxis. Given our ability to treat infected patients and the risks and costs of antibiotic resistance, the practice of antibiotic prophylaxis for children with measles does not seem justified no matter what the value (either numeric or otherwise) of the summary odds ratio.

1 McIntosh MW. The population risk as an explanatory variable in research synthesis of clinical trials. *Stat Med* 1996;15:1713-28.

University of Pennsylvania School of Medicine, Center for Clinical Epidemiology and Biostatistics, 423 Guardian Drive, Philadelphia, PA 19104-6021, USA

Jesse A Berlin *associate professor of biostatistics*

berlin@cceb.med.upenn.edu

A MOST UNFORTUNATE NEEDLESTICK INJURY

Why the doctor paid a taxi for the nurse

A few months ago when I was inserting an intravenous catheter into the cubital vein of a patient with malaria I accidentally stung the assisting nurse in the back of her hand with the needle that was withdrawn from the catheter. As the nurse had an adequate hepatitis B vaccination titre I advised her to contact me only if she developed fever. Eighteen days later she called and said that she had flu. I asked her to come to the hospital for a thick smear, but she wanted to go to bed and take some aspirin. Besides, she was alone at home and had no money for transport. Afraid of the possible consequences of her staying at home and feeling guilty, I offered to pay for a taxi.

On examination she had a temperature of 39.5°C without any other abnormal findings. A thick smear showed two ring stages of *Plasmodium falciparum* per 100 leucocytes. The number of leucocytes was 2.8×10^9/l, the other laboratory results were normal. She was treated with 600 mg of oral quinine three times a day for three days and three tablets of Fansidar on the third day. She recovered well.

The patient with malaria had acquired her infection in the Gambia. She had not taken any antimalarial medication at the time of the accident when her parasitaemia was 277/100 leucocytes (= 0.2% parasitised red blood cells). Despite this low grade of parasitaemia and the minimal transfusion of blood from the patient to the nurse, transmission apparently took place. If you assume entrance of one single, parasitised red blood cell into the circulation and a multiplication factor of 10 every two days you can expect a total of 10^9 parasites at day 18. Assuming no sequestration you would expect a parasitaemia of about 7/100 leucocytes.

The case teaches us that the normal incubation period for *P falciparum* malaria (10 to 16 days) does not apply in cases of needlestick malaria. Since the liver stage is bypassed it may be as short as seven days but with a very small inoculum symptoms can start 18 days after the accident, as seen in our patient. Previous reports on accidental inoculations showed incubation periods varying from seven to 17 days and up to 24 days in case of blood transfusions.

It would probably have been a safer course of action, however, to have treated the nurse immediately after the injury.

Michael A Van Agtmael *is an internist in the department of infectious diseases, tropical medicine and AIDS of the Academic Medical Centre, Amsterdam, Netherlands*

Respiratory morbidity 10 years after the Union Carbide gas leak at Bhopal: a cross sectional survey

P Cullinan, S Acquilla, V Ramana Dhara, on behalf of the International Medical Commission on Bhopal

Department of Occupational and Environmental Medicine, Imperial College (National Heart and Lung Institute), London SW3 6LR

P Cullinan, *senior lecturer*

Department of Epidemiology and Public Health, University of Newcastle upon Tyne, Newcastle upon Tyne NE2 4HH

S Acquilla, *lecturer*

Agency for Toxic Substances and Disease Registry, E-31, 1600 Clifton Road, Atlanta 30333, Georgia, USA

V Ramana Dhara, *visiting scientist*

BMJ 1997;314:338–43

Abstract

Objective: To examine the role of exposure to the 1984 Bhopal gas leak in the development of persistent obstructive airways disease.
Design: Cross sectional survey.
Setting: Bhopal, India.
Subjects: Random sample of 454 adults stratified by distance of residence from the Union Carbide plant.
Main outcome measures: Self reported respiratory symptoms; indices of lung function measured by simple spirometry and adjusted for age, sex, and height according to Indian derived regression equations.
Results: Respiratory symptoms were significantly more common and lung function (percentage predicted forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), forced expiratory flow between 25% and 75% of vital capacity (FEF_{25-75}), and FEV_1/FVC ratio) was reduced among those reporting exposure to the gas leak. The frequency of symptoms fell as exposure decreased (as estimated by distance lived from the plant), and lung function measurements displayed similar trends. These findings were not wholly accounted for by confounding by smoking or literacy, a measure of socioeconomic status. Lung function measurements were consistently lower in those reporting symptoms.
Conclusion: Our results suggest that persistent small airways obstruction among survivors of the 1984 disaster may be attributed to gas exposure.

Introduction

In the early hours of 3 December 1984 an explosion at the Union Carbide India pesticide plant in Bhopal, Madhya Pradesh, India, resulted in about 27 tonnes of toxic gas being dispersed over the city. The exact nature of the gas remains disputed, but most of it was probably methyl isocyanate, a pungent gas of low boiling point (39°C) and high vapour pressure (348 mm Hg at 20°C).[1] There is little non-anecdotal information on the subsequent path of the gas plume, though attempts to model its dispersion using the scanty meteorological data available suggest that it travelled slowly southwards from the plant.[2] About a quarter of the city's million inhabitants are believed to have been exposed.

The acute effects of heavy exposure were consistent with inhalation of a volatile (and deeply penetrating), highly irritative aerosol; large numbers of people died rapidly with bronchial necrosis or pulmonary oedema.[3] Within months of the disaster clinical, radiological, and pathological evidence suggested survivors had persistent airflow obstruction associated with an obliterative bronchiolitis.[4] Subsequent case reports have proposed other pulmonary outcomes including interstitial fibrosis.[5] However, there have been no published systematic studies of the long term respiratory effects of exposure to the gas leak.

We describe findings from a survey conducted 10 years after the disaster at the request of community groups in Bhopal. An earlier paper documented the wide variety of symptoms reported by those exposed to the gas leak.[6] Here we present a detailed analysis of respiratory symptoms and function among a random sample of survivors in which the role of gas exposure has been assessed by examining its relation with disease frequency.

Subjects and methods

To ensure that we selected subjects with different levels of exposure we created four concentric zones of 2, 4, 6, and 8 km radius centred on the Union Carbide factory site using a map of the city. We also examined an area outside the city but of similar socioeconomic composition to the urban zones to act as an unexposed control zone. From each of these areas we surveyed a sample of the current resident population by selecting houses using random numbers from two electoral wards on either side of a straight line south from the factory site. We invited (after random selection from a hat) one of the adults (18-60) present who had been resident in Bhopal in 1984 to complete a questionnaire.

The previously piloted structured questionnaire was administered in Hindi by trained interviewers and inquired into details of exposure to the gas leak, current and past health, and socioeconomic factors. Place of residence at the time of the gas leak was confirmed from official records held by each of those interviewed. Subjects were defined as dyspnoeic if they reported breathlessness either when walking on level ground or on climbing hills. Literacy was defined as the completion of at least primary education. Men with low incomes were those with no paid work or a monthly wage of less than 500 rupees (about £10).

We invited a 20% random sample of those interviewed to undergo spirometry using a rolling seal spirometer (Ohio 822, National Institute for Occupational Safety and Health, United States). After instruction from an experienced doctor subjects carried out at least two acceptable and reproducible manoeuvres[7] before and after inhalation of 200 µg of salbutamol. The instrument was calibrated and checked for leaks before and after each day's session. Measurements of forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), FEV_1/FVC, and forced expiratory flow between 25% and 75% of vital capacity (FEF_{25-75}) were corrected for body temperature, pressure, and saturation and expressed as proportions of predicted values by using regression equations for Central Indian adults provided by Udwadia *et al.*[8]

We analysed symptoms and lung function measurements according to whether the subject reported

exposure to the gas leak. More detailed exposure-response relations were examined by estimating exposure expressed as the distance from the factory of the central point of the electoral ward in which the subject was living at the time of the disaster; this index was grouped before analysis according to roughly equal sized categories of increasing exposure.

We assessed differences in proportions between categorical variables by χ^2 statistics and χ^2 tests for linear trend using EGRET and EPI-INFO 6 statistical software. Associations between lung function and estimated exposure (expressed continuously by distance of ward from the factory) were examined by linear regression.

Results

A total of 454 subjects were interviewed (no selected subjects declined an interview) and 74 (82% of those eligible) underwent spirometry. Table 1 shows the distribution of subjects by estimated exposure and potentially confounding variables. Only five of the 14 subjects in the control area attended for lung function testing. There were no important or consistent differences in the age, sex distribution, socioeconomic status, or reporting of cough, sputum, or breathlessness between those who did and did not attend for testing. One person was unable to perform satisfactory lung function measurements.

There were close relations between sex and low income (most women were not in paid work) and smoking (only two women reported ever smoking). All but two of those who reported ever having smoked were current smokers. The proportions of illiterate subjects and low income men in the high exposure categories tended to be greater than in the non-exposed groups, but the trends were not consistent. There was no such gradient with smoking. Although numbers were small, similar trends were discernible among those undergoing spirometry. Smoking was not significantly associated with literacy ($\chi^2 = 0.5$, $P = 0.480$).

Of those who reported exposure to the gas leak, 190 (54%) described a cough and 54 (15%) phlegm production for at least three months each year. Two hundred and ninety four (84%) reported dyspnoea and 30 (9%) wheeze in the past 12 months. These frequencies were significantly higher ($P<0.001$) than those in people who were unexposed (16 (16%), 3 (3%), 55 (54%), and 1 (1%) respectively), and the differences remained when literate subjects or those who had never smoked were examined separately.

Table 1 Demographic characteristics of interviewed and tested subjects according to distance lived from Union Carbide plant

	Distance (km)						
	0-2	2-4	4-6	6-8	8-10	>10	P value*
Interviewed subjects:							
No	97	75	72	52	81	75	
Mean age (years)	38	39	36	39	37	38	
No (%) men	31 (32)	33 (44)	26 (36)	25 (48)	35 (43)	46 (61)	<0.001
No (%) literate	33 (34)	49 (65)	32 (44)	11 (21)	33 (41)	43 (57)	0.416
No (%) with low income†	17 (55)	16 (48)	9 (35)	16 (64)	13 (37)	15 (33)	0.061
No (%) ever smoked†	12 (39)	5 (15)	4 (15)	10 (40)	11 (31)	22 (48)	0.690
Tested subjects:							
No	21	13	18	8	9	5	
Mean age (years)	36	36	39	33	39	30	
No (%) men	9 (43)	5 (38)	5 (28)	5 (63)	2 (22)	4 (80)	0.583
No (%) literate	6 (29)	8 (62)	6 (33)	1 (13)	2 (22)	5 (100)	0.428
No (%) with low income†	6 (67)	2 (40)	3 (60)	4 (80)	2 (100)	1 (25)	0.893
No (%) ever smoked†	5 (56)	5 (100)	3 (60)	3 (60)	1 (50)	2 (50)	0.218

*χ^2 test for linear trend.† Men only.

A more detailed analysis revealed consistent and significant trends in each symptom across six categories of estimated exposure (fig 1). These trends were equally strong ($P<0.001$ for each group) in men and women, and more so in those aged less than 35 years, the median age of the group. All symptoms were reported more often by cigarette smokers but were still common in non-smokers; after those who had ever been smokers were excluded the associations between

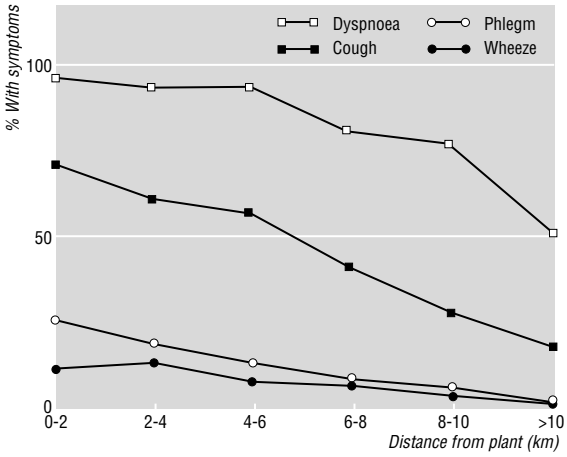

Fig 1 Trends in reported respiratory symptoms according to distance lived from Union Carbide plant

Table 2 Number (percentage) of subjects with respiratory symptoms according to distance lived from Union Carbide plant

	All subjects (%)					Never smoked (%)				Literate (%)			
Distance from plant (km)	No of subjects	Cough for >3 months	Phlegm for >3 months	Dyspnoea	Wheeze in past year	No of subjects	Cough for >3 months	Phlegm for >3 months	Dyspnoea	No of subjects	Cough for >3 months	Phlegm for >3 months	Dyspnoea
0-2	97	69 (71)	25 (26)	92 (95)	12 (12)	85	58 (68)	19 (22)	80 (94)	33	21 (64)	5 (15)	33 (100)
2-4	75	45 (60)	14 (19)	69 (92)	10 (13)	70	41 (59)	12 (17)	64 (91)	49	27 (55)	8 (16)	44(90)
4-6	72	40 (56)	9 (13)	66 (92)	5 (7)	67	38 (57)	9 (13)	61 (91)	32	18 (56)	7 (22)	31(97)
6-8	52	21 (40)	4 (8)	41 (79)	3 (6)	42	18 (43)	2 (5)	35 (83)	11	3 (27)	0 (0)	8(73)
8-10	81	22 (27)	4 (5)	61 (75)	2 (3)	70	19 (27)	4 (6)	54 (77)	33	7 (21)	0 (0)	24(73)
>10	75	13 (17)	1 (1)	37 (49)	0 (0)	52	7 (13)	1 (2)	25 (48)	43	8 (19)	1 (2)	17(40)
P value*		<0.001	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001		<0.001	0.002	<0.001

*χ^2 test for linear trend.

Table 3 Mean percentage of predicted lung function values by reported and estimated gas exposure*

	No of subjects	FEV_1	FVC	FEF_{25-75}	FEV_1/FVC
All subjects					
Exposed	63	103	100	89	98
Unexposed	7	106	99	106	102
Distance from plant (km):					
0-2	20	98	97	84	97
2-6	31	105	103	88	98
6-10	17	105	98	101	100
>10	5	112	104	123	105
Never smoked					
Exposed	54	102	99	90	99
Unexposed	5	98	95	89	100
Literate					
Exposed	22	96	98	78	94
Unexposed	6	111	105	115	103

*Where totals do not correspond exactly information on reported exposure was missing.

symptoms and reported or estimated exposure remained (table 2). Similar results were obtained when literate subjects or men with low incomes (data not shown) were examined alone, though the numbers in each group were small and the gradients less consistent.

Before we analysed lung function and exposure among those tested we collapsed the four estimated exposure categories based on distance from the plant. All indices of pulmonary function were lower in those reporting exposure to the gas and among those in the higher categories of estimated exposure (table 3, fig 2). When distance was analysed as a continuous variable FEF_{25-75} was significantly reduced ($P = 0.004$) but no association was found for the other indices of lung function ($P > 0.05$). We also divided measurements of function into equal quartiles; seven (35%) of those in the 0-2 km exposure category had an FEF_{25-75} result in the lowest quartile (<67% predicted), compared with nine (29%), three (18%), and zero in the 2-6 km, 6-10 km, and >10 km categories respectively. The equivalent proportions were six (29%), eight (26%), four (24%), and zero for FEV_1/FVC ratio; seven (33%), seven (23%), four (23%), and one (20%) for FEV_1; and six (29%), four (19%), five (29%), and one (20%) for FVC. Stratification according to smoking habit or socioeconomic factors (literacy or, in men, low income) weakened but did not abolish the relations with reported exposure. There were too few subjects to adjust simultaneously for these factors and for estimated exposure.

Table 4 Mean percentage predicted lung function by reported symptoms

	No of subjects	FEV_1	FVC	FEF_{25-75}	FEV_1/FVC
Cough for >3 months:					
Yes	39	97	95	87	97
No	31	108	104	94	100
Phlegm for >3 months:					
Yes	41	99	95	92	98
No	31	104	100	93	100
Dyspnoea:					
Yes	14	102	99	89	98
No	59	111	106	107	102
Wheeze:					
Yes	5	94	102	53	85
No	68	104	100	95	100

Lung function values among those reporting respiratory symptoms were consistently reduced (table 4) as they were among cigarette smokers. Only two subjects (both exposed to gas) had an increase in FEV_1 of 200 ml (and at least 15%) after administration of salbutamol.

Discussion

We have shown an excess of respiratory symptoms and a reduction in mean lung function among those reporting exposure to the Bhopal gas leak in 1984. We have also shown a direct gradient in effects according to an estimate of the intensity of gas exposure. We studied people still resident in Bhopal 10 years after the gas leak and thus their symptoms cannot represent the acute or long term lethal effects of gas exposure in the intervening decade. The symptoms reported, and differences in lung function detected, are compatible with chronic airflow limitation and particularly with disease of the small airways.

Validity

Several features suggest that the relation between the symptoms and exposure to the gas leak was causal rather than a chance association. Firstly, our findings are plausible: the physical characteristics of methyl isocyanate suggest that airborne droplets would have vaporised after inhalation and penetrated deep into the bronchial tree. Secondly, there was a high internal consistency in responses to our questionnaire and between these and the results of spirometric testing. Thirdly, we have shown a dose-response effect in both symptoms and lung function. In the absence of a validated respiratory symptom questionnaire for these circumstances and of an objective measurement of abnormal lung function we relied on internal comparisons to assess the relation between gas exposure and outcome.

We deliberately used a crude estimate of gas exposure, relying on addresses at the time of the leak, in the belief that these would be readily recalled and less liable to misclassification than more complex indices. Though place of residence at the time of the leak was

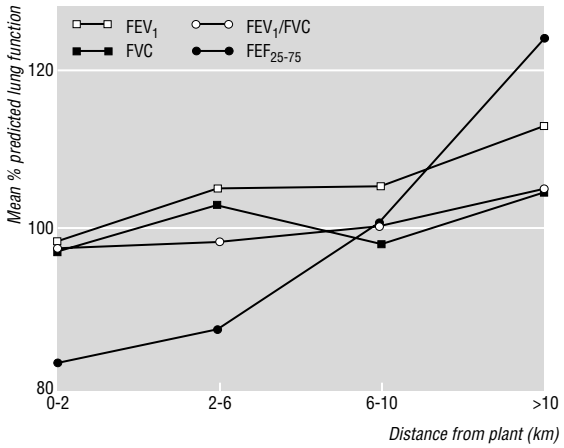

Fig 2 Relation between respiratory function and distance lived from Union Carbide plant

established objectively, self reported symptoms are open to recall bias. However, the associations between the frequency of reported symptoms and estimated exposure were striking, and the consistency of the symptom gradients across narrow (2 km) bands of estimated exposure supports our belief that these findings are not wholly explained by differential reporting. Similar gradients were found for the results of lung function testing; there were no obvious differences between those invited for testing who did and did not attend, but the variability in response between exposure groups and the small numbers involved necessitate cautious interpretation. To account for the different age, sex, and height distributions across exposure categories we adjusted the measurements using regression equations derived from an Indian population. Despite this the derived figures should be treated as relative rather than absolute values.

The issue of confounding by other factors is unavoidable. We addressed this by stratifying analyses according to various potential confounding variables. Although the exposure relations tended to be weaker after stratification, this exercise suggested that a proportion of the observed relations can be attributed directly to gas exposure. In an earlier study three years after the gas leak, Andersson *et al* reported a relation between estimated exposure and respiratory symptoms which could not be accounted for by age or cigarette smoking.[9] We remain aware, however, of the difficulties of completely expressing the effect of confounding variables—particularly those which reflect socioeconomic factors such as low birth weight.[10]

Key messages

- Many people died as a result of exposure to gas after the 1984 Union Carbide disaster in Bhopal but long term effects remain unclear
- In this study respiratory disease attributable to gas exposure was detected in adult survivors
- The frequency of symptoms decreased with decreasing exposure (as estimated by distance of home from the plant)
- Lung function showed similar trends, although the number of subjects was much smaller
- Much of the disease is probably due to irreversible obstruction in small airways

Other studies

Previous studies of respiratory morbidity in Bhopal survivors have not examined disease beyond two or three years after the disaster. Rastogi *et al* examined lung function in 783 exposed volunteers and detected severe respiratory impairment (reductions in FEV_1 or FVC, or both) in 2.4%, mainly of a mixed obstructive-restrictive nature.[11] They did not attempt to correlate their findings with a measure of exposure. Kamat and colleagues followed 113 subjects who had been initially admitted to hospital.[12] Over two years they found no improvement in respiratory symptoms or in basic spirometry, but 42% of the group had evidence consistent with deteriorating small airways function. It is difficult to estimate how much of this could be attributed to gas exposure. Bronchoalveolar lavage in 36 subjects one to two and a half years after the leak showed increased cellularity (macrophages or neutrophils, or both) in those who were severely exposed (as assessed by immediate morbidity), a finding which could not be wholly attributed to smoking[13] and which the authors suggested was consistent with a subclinical alveolitis.

Our long term findings are consistent with small airways obstruction and with the obliterative bronchiolitis reported among early survivors.[4] Similar effects have been reported following accidental inhalation of other irritant gases.[14 15] Long term obstructive changes in spirometry have also been described in seven Finnish miners exposed to high concentrations of (mainly) sulphur dioxide, in whom measurements of lung function before exposure were available; mean FEV_1 was 13% below predicted after four years with a smaller proportional reduction in FVC.[16] Persistent obstruction after exposure to an irritant is probably the result of repair processes after initial epithelial and basement membrane damage, the level of obstruction being determined by the site of maximal bronchial deposition, which is determined largely by the physicochemical characteristics of the irritant. Irritant induced asthma (or reactive airways dysfunction syndrome) has also been described after high intensity exposures[17] and was reported in four of the Finnish miners.[16] Although we did not conduct formal tests of histamine or metacholine reactivity, the lack of response to salbutamol in all but two of our subjects suggests that this is not a common outcome in survivors of the Bhopal gas leak.

Implications

The dearth of rigorous examinations of the relation between exposure to the gas and subsequent morbidity is one of the lesser tragedies of the Bhopal disaster. One result is that the establishment of appropriate models of health care and the equitable distribution of available compensation have been hampered. We did not attempt formal measurement of exercise capacity, but several subjects reported being too breathless to undertake paid employment. Though there was little evidence in this group that the airflow obstruction was reversible by simple bronchodilators, many were taking prescribed (and often expensive) medicines inappropriately—for example, haphazard courses of systemic steroids and a variety of (mainly oral) bronchodilators.

Our findings suggest the need for further, locally initiated studies of the extent of persistent airflow obstruction attributable to gas exposure and for controlled trials of effective treatments. This small study, carefully planned but completed in nine days, is a model for low cost and low technology research into the long term effects of the gas leak. Similar studies might usefully concentrate on respiratory disease in those who were infants at the time of the disaster as well as effects on other (for example, ocular and neurological) systems.

Other members of the International Medical Commission on Bhopal were R Bertell (Canada), T Calender (USA), I Eckerman (Sweden), J Havens (USA), B Heinzow (Germany), J

Jaskowski (Poland), C Sathymala (India), L Titov (Byelorussia), G Tognoni (Italy), M Verweij (Netherlands), W Zhengang (China).

We thank Satinath Sarangi, Bhopal Gas Peedith Mahila Udyag Sanghatana, Gas Peedith Stationary Karamchari Sangh, and Zahreeli Gas Kand Sangharsh Morcha, Dr Isobel Gillis, Dr Eugene Milne, Mr Adrian Cook, and Professor A J Newman Taylor for their help. The spirometer was kindly loaned by the division of respiratory diseases, National Institute for Occupational Health, Morgantown, USA.

Funding: The commission was funded by Christian Aid (UK), Greenpeace and Bread for the World (Germany), United Council of Churches in Christ (USA), and other environmental and religious charities.

Conflict of interest: None.

1 Carbide Corporation. *Bhopal methyl isocyanate incident investigation team report.* Danbury, Connecticut, US: Union Carbide Corporation, 1985.
2 Singh MP, Ghosh S. Bhopal gas tragedy: model simulation of the dispersion scenario. *J Hazardous Mat* 1987;17:1-21.
3 Indian Council of Medical Research. *Health effects of exposure to toxic gas at Bhopal: an update on ICMR sponsored researches.* New Delhi: ICMR, 1985.
4 Weill H. Disaster at Bhopal: the accident, early findings and respiratory health outlook in those injured. *Bull Eur Physiopathologie Respiratoire* 1987;23:587-90.
5 VK, Sankaran K, Sharma SK, Misra NP. Chronic lung inflammation in victims of the toxic gas leak at Bhopal. *Resp Med* 1995;89:105-11.
6 Cullinan P, Acquilla SD, Dhara VR. Long term morbidity in survivors of the 1984 Bhopal gas leak. *Natl Med J India* 1996;9:5-10.
7 American Thoracic Society. Standardisation of spirometry: 1987 update. *Am Rev Resp Dis* 1987;136:1285-96.
8 Udwadia FE, Sunavala JD, Shetty VM. Lung function studies in healthy Indian subjects. *J Assoc Physicians India* 1987;36:454-7.
9 Andersson N, Ajwani MK, Mahashabde S, Tiwari MK, Kerr Muir M, Mehra V, *et al.* Delayed eye and other consequences from exposure to methyl isocyanate: 93% follow-up of exposed and unexposed cohorts in Bhopal. *Br J Ind Med* 1990;47:553-8.
10 Barker DJP, Godfrey KM, Fall C, Osmond C, Winter PD, Shaheen SO. Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. In: Barker DJP, ed. *Fetal and neonatal origins of adult disease.* London: BMJ Publishing, 1992:150-6.
11 Rastogi SK, Gupta BN, Husain T, Kumar A, Chandra S, Ray PK. Effect of exposure to toxic gas on the population of Bhopal. II. Respiratory impairment. *Ind J Exp Biol* 1988;26:161-4.
12 Kamat SR, Patel MH, Pradhan PV, Taskar SP, Vaidya PR, Kolhatkar VP, *et al.* Sequential respiratory, psychologic and immunologic studies in relation to methyl isocyanate exposure over two years with model development. *Env Health Perspectives* 1992;97:241-53.
13 Vijayan VK, Pandey VP, Sankaran K, Mehrotra Y, Darbari BS, Misra NP. Bronchoalveolar lavage study in victims of toxic gas leak at Bhopal. *Ind J Med Res* 1989;90:407-14.
14 Darke CS, Warrack AN. Bronchiolitis from nitrous fumes. Thorax 1958;13:327-33.
15 Galea M. Fatal sulphur dioxide inhalation. *Can Med Assoc J* 1964;91:345-7.
16 Harkonen H, Nordman H, Korhonen O, Winblad I. Long-term effects of exposure to sulphur dioxide. *Am Rev Resp Dis* 1983;126:890-3.
17 Brooks SM, Weiss MA, Bernstein IL. Reactive airways dysfunction syndrome (RADS): persistent asthma after high-level irritant exposures. *Chest* 1985;88:376-84.

(Accepted 15 November 1996)

Commentary: Industry can damage your health

Paul Garner

Liverpool School of Tropical Medicine, University of Liverpool, L3 5QA
Paul Garner, *head of the international health division*

Poverty causes disease, and specialists view economic growth as central to good health in poor countries.[1] Industry is a mainstay of development, yet converting labour from a social property to an adjunct of capital has adverse consequences.[2] The lasting image of Bhopal, the cloud of poisonous gas from a multinational company that left thousands of people dead and many more injured, should remind us all that industry can kill and maim the very groups that development is supposed to benefit. We are still discovering long term injury from that event in Bhopal 12 years ago.

Industrial risk in poor countries is vast: exposure ranges from dangerous glues used to make shoes in shanty huts to unsafe steel smelting plants.[3] Bhopal was an extreme example, but every day in developing countries there are a wide range of industrial accidents in the workplace, and people are poisoned over many years by industrial pollution.[4] Yet sometimes those in authority play down these risks: in the occupational health section of the *World Development Report* the World Bank starts with deficient household water and sanitation for women who work at home, move to agriculture, and end without once mentioning the word industry.[1] In contrast, the World Health Organisation points out that in most developing countries there are no effective legal or institutional structures to deal with pollution in the workplace and surrounding areas.[3] The chasm in this area of public health is frightening, particularly as exposure will become more intense as industry develops and more of the world's poor come to live in cities.[5]

Much could be done in developing countries immediately to reduce occupational and local environmental risks from industry without awaiting further research. Studies that simply describe the extent of industry related exposure to harmful agents in developing countries assist advocacy for effective legislation. Cullinan *et al* show how much valuable epidemiological information can be generated with limited resources. Unfortunately, few studies have been reported. Medline (1991-5) lists only three articles about diseases related to Bhopal, in a total of 269 exposed people; whereas there are eight big studies on Sellafield (United Kingdom), one of which follows over 75 000 people.

Industry invests in science to maximise profit, but there should be an equal investment to protect the public, wherever they live. The injustice is worse when the profiting elite do not even live in the country that their industry is damaging. Any organisation promoting or participating in economic development in poor countries has a moral responsibility to ensure they do not risk the health of the majority for the benefit of a few.

1 The World Bank. *World development report 1993. Investing in health.* New York: Oxford University Press, 1993:6, 95-6.
2 Braverman H. *Labor and monopoly capital.* New York: Monthly Review Press, 1974:45-58.
3 World Health Organisation. *Our planet, our health. Report of the WHO Commission on health and the environment.* Geneva: World Health Organisation, 1992:175-96.
4 Weir D. *The Bhopal syndrome. Pesticides, environment and health.* London: Earthscan Publications, 1988:IX-XII.
5 McMichael AJ. *Planetary overload. Global environmental change and the health of the human species.* Cambridge: Cambridge University Press, 1993:13.

Commentary: Assessing the effects of environmental pollution when people know that they have been exposed

R T Mayon-White

Acute episodes of massive air pollution with harmful effects are fortunately rare, but this means that no one is very experienced at investigating such risks. The immediate effects may be blast and burns injuries, acute chemical toxicity as at Bhopal in 1984, irritation causing acute respiratory and conjunctival symptoms, or the sight and smell of smoke and fumes causing fear. The suddenness and speed at which the pollution arises, usually in an explosion or a fire, give little chance of collecting data before exposure. Epidemiological studies into the longer term effects have to be done after the pollution has dispersed and when public opinion has formed about the expected health effects. Investigations may be made more difficult if there is little toxicological knowledge of the long term effects of a single exposure or if the pollutants are not fully identified.

So the investigation into the long term effects of a relatively brief exposure to airborne chemicals is an exploration, not a well trodden path. However, if the dramatic circumstances of incidents like Bhopal are set aside, the epidemiological task is the familiar problem of deciding whether there is an association between an environmental factor and ill health, and if any relation is cause and effect.

The study by Cullinan *et al* is a good example of what can be achieved with modest resources. Cross sectional studies are usually much cheaper than cohort studies in which a population (or sample) is followed for years to assess the effects of differing levels of exposure. Without detailed information on where the toxic gas plume went and where subjects were at the time, the distance between the Union Carbide factory and the home of the subject is a simple way of grading exposure, and better than the subjects' own impressions. A random sample was essential, but a bias could occur if people with respiratory symptoms were more or less likely than others to move away from the area. In some situations the subjects might be asked if they stayed indoors, as another way of getting different degrees of exposure.

In any study where both the subjects and the investigators are aware of their exposure, and the possible illness, the investigators need objective measurements of health: the lung function tests in the Bhopal study. As shown here, symptoms should not be dismissed as subjective and biased as sceptics might suppose. If symptoms can be compared with physiological or pathological tests in a subset of subjects the strength of large numbers studied by questionnaire can be exploited. In assessing the statistical association for cause and effect the strength of the association, the specificity of the medical condition, the biological gradient, the biological plausibility, and the coherence of the evidence are clear. The results fit with earlier studies in Bhopal but there are, fortunately, no other similar incidents which would test the consistency of the association. The relation with time cannot be assessed by one cross sectional study, and no experimental evidence or analogies apply. I am convinced by the evidence that the gas from Bhopal has caused chronic obstructive airways disease and I value this paper as a useful example of how to look for the damage that may be caused by a chemical disaster.

Directorate of Public Health and Health Policy, Oxfordshire Health Authority, Oxford OX3 7LG

R T Mayon-White, *consultant public health physician*

Follow up policy after treatment for Hodgkin's disease: too many clinic visits and routine tests? A review of hospital records

J A Radford, A Eardley, C Woodman, D Crowther

Abstract

Objective: To examine the effectiveness of routine clinic review in detecting relapse after treatment for Hodgkin's disease.
Design: Review of hospital records.
Setting: Regional centre for cancer treatment and research.
Subjects: 210 patients with Hodgkin's disease recruited to a chemotherapy trial protocol between 1984 and the end of 1990 who had achieved a complete or partial remission after treatment.
Main outcome measures: The number of clinic visits made by patients over the period of observation, the number of relapses occurring during that time, and the route by which relapse was detected.
Results: The 210 patients generated 2512 outpatient reviews, and 37 relapses were detected. Thirty relapses (81%) were diagnosed in patients who described symptoms, which in 15 cases had resulted in an earlier appointment being arranged. In only four cases (11%; 95% confidence interval 4% to 25%) was relapse detected as a result of routine physical examination or investigation of a patient who did not have symptoms.
Conclusions: Relapse of Hodgkin's disease after treatment is usually detected as a result of the investigation of symptoms rather than by routine screening of asymptomatic patients. It is therefore

Cancer Research Campaign Department of Medical Oncology, Christie Hospital NHS Trust, Manchester M20 4BX

J A Radford, *senior lecturer in medical oncology*

D Crowther, *professor of medical oncology*

BMJ 1997;314:343–6

continued over

Centre for Cancer Epidemiology, Christie Hospital NHS Trust, Manchester M20 4BX

A Eardley, *clinical audit and quality assurance facilitator*

C Woodman, *professor of cancer epidemiology*

Correspondence to: Dr Radford.

proposed that the frequency of routine follow up visits should be reduced and greater emphasis placed on patient education. This should underline the importance of symptoms and encourage patients to arrange an earlier appointment if these develop.

Introduction

After treatment for Hodgkin's disease it is routine for patients to be reviewed in the clinic on a regular basis. A main purpose is to detect relapse at an early stage, when the tumour burden is light and salvage therapy is considered to have the best chance of effecting a cure. To our knowledge, however, the effectiveness of routine clinic review in detecting recurrent Hodgkin's disease has not been examined. We report such a study in a cohort of 210 patients treated at this hospital.

Patients and methods

Follow up

Between 1984 and the end of 1990, 254 patients referred to this hospital with high risk stages I and II (presence of B symptoms or bulky mediastinal tumour, or both) and stages III and IV Hodgkin's disease were randomised in a collaborative phase III trial comparing mustine, vinblastine, procarbazine, and prednisone chemotherapy with a seven drug hybrid regimen (chlorambucil, vinblastine, procarbazine, and prednisolone and etoposide, vincristine, and doxorubicin). After chemotherapy patients in complete or partial remission received radiation treatment to sites of initial bulk disease or to areas of residual abnormality on the restaging computed tomography scan. Thirty patients either did not respond, had progression of their disease, or died during treatment and are not considered further. Full details of chemotherapy and radiotherapy, remission rates, causes of early death, progression free survival, and survival have been reported.[1]

The frequency of follow up visits for patients in remission after initial treatment accorded with current Manchester Lymphoma Group policy and Cotswold committee recommendations[2]—namely, two monthly visits in year 1, three monthly visits in year 2, four monthly visits in year 3, six monthly visits in years 4 and 5, and yearly visits thereafter. On each occasion patients are asked about symptoms and examined for evidence of recurrent disease. Blood is drawn for a blood count, the erythrocyte sedimentation rate, and a serum biochemical profile, and if the patient had mediastinal disease at presentation a chest radiograph is obtained. Other investigations are arranged as clinically indicated.

We examined the case notes of 210 of the 224 patients who achieved complete or partial remission with chemotherapy alone or chemotherapy plus radiotherapy and who were therefore eligible for outpatient review. Of the remaining 14 patients, eight lived far from the hospital and had been followed up by a local physician, one had emigrated, and case notes for the remaining five were unavailable.

The number of clinic visits during each of the first five years of follow up for 210 patients was recorded by a data abstractor and the case notes of patients who had relapsed put aside for further scrutiny. The second phase of the study was performed by three of us (JR, AE, and CW), who identified the following information for each relapsing patient: (*a*) the clinic visit that led directly to the diagnosis of relapse; (*b*) whether that visit was a routine appointment or one arranged by the patient, a relative, or another doctor because of the onset of symptoms; (*c*) whether it was a symptom volunteered by the patient, a sign identified on physical examination, or the result of a routine investigation in an asymptomatic patient that led directly to the diagnosis of relapse.

Table 1 Symptoms reported by 30 patients found to have recurrent Hodgkin's disease

Symptoms	No of patients affected †
Lump	10
Cough	7
Night sweats	6
Weight loss	6
Itching	3
Lethargy	3
Breathlessness	3
Chest pain	3
Abdominal pain	3
Back pain	2
Fever	2
Sore mouth or throat	2
Shoulder pain	1
Alcohol induced pain	1
Loss of appetite	1
Rash	1

† Thirteen patients reported one symptom, 10 patients reported two symptoms, and seven patients reported three or more symptoms.

Risk of relapse

Estimates of how relapse rates varied over time were obtained by kernel smoothing[3] of data for 369 patients achieving complete or partial remission after treatment in the collaborative trial[1] from which the 224 patients for this study were derived.

Results

Outpatient review and relapse

Over the period of observation the 210 patients generated 2512 outpatient reviews (1086 in year 1, 667 in year 2, 420 in year 3, 231 in year 4, 108 in year 5), and 37 relapses were detected—a ratio of one relapse detected for every 68 visits. Thirty relapses (81%) were diagnosed in patients who described a symptom or symptoms which in 15 cases had resulted in an earlier appointment being arranged either by the patient or by a close relative (n = 10) or by a local doctor (n = 5). Thirteen of 30 patients reported one symptom, 10 patients reported two symptoms, and seven patients reported three or more symptoms (maximum five). Presence of a lump (n = 10), cough (n = 7), night sweats (n = 6), and weight loss (n = 6) were the most frequently reported symptoms (table 1).

In four cases (11%; 95% confidence interval 4% to 25%) relapse was detected as a result of routine physical examination or investigation of a patient who did not have symptoms (palpable lymphadenopathy (two cases), abnormal chest radiograph (two cases)). In a further three patients the case notes were unclear whether symptoms had been present. Figure 1

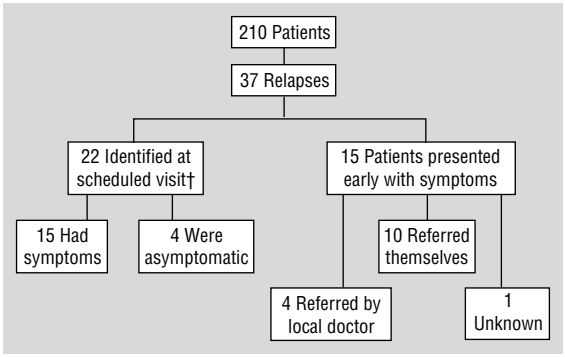

Fig 1 Flow chart showing relation of relapse, presence of symptoms, and visits to clinic for 210 patients followed up after treatment for Hodgkin's disease
†Presence or absence of symptoms unclear from case notes in three cases.

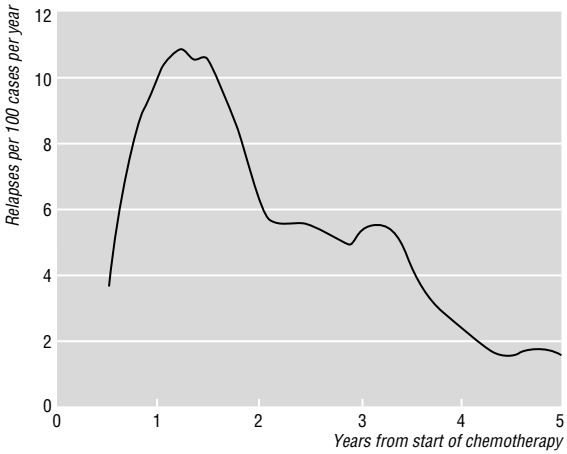

Fig 2 Kernel smoothed estimates of relapse rates over time for 369 patients in complete or partial remission after treatment for Hodgkin's disease. Epanechnikov kernel and a nine month bandwidth were used

summarises the relation between relapse, presence or absence of symptoms, and whether or not the clinic visit was as previously arranged or early.

Risk of relapse

Figure 2 shows the variation of relapse rates over time in 369 patients. Risk of relapse was not uniform over the period of follow up with a peak of 10 or 11 events per 100 patients yearly occurring 12-18 months after the start of treatment with a rapid decline to about five relapses per 100 patients yearly by year 3 and a further fall to fewer than two relapses per 100 patients yearly by year 5.

Discussion

Routine review after treatment for Hodgkin's disease has several functions, including patient reassurance, detection of second tumours, and monitoring the late effects of chemotherapy and radiotherapy on gonadal, cardiac, and pulmonary function. Probably the most important function, however, is the early diagnosis of relapse. In this study 37 relapses were detected in 210 patients by using a follow up policy that generated a total of 2512 hospital visits during the period of observation. Of particular interest, 30 (81%) of the 37 patients in whom relapse was diagnosed had symptoms and in only four cases (11%) was relapse detected in an asymptomatic patient either by physical examination (two cases; 5.4%) or by a routine screening test (two cases; 5.4%). Furthermore, 15 of the 30 patients with symptoms either arranged an earlier clinic appointment for themselves or sought the advice of a local doctor, who arranged an earlier appointment on their behalf.

These findings are closely similar to those of Weeks *et al*, who studied follow up policy after chemotherapy for large cell lymphoma.[4] They found that 32 of 36 relapses (89%) were detected because of symptoms and that only two relapses (5.6%) were diagnosed from an abnormal screening test result in an asymptomatic patient. A notable difference between the two studies was that in the American series all 32 patients with symptoms arranged an earlier clinic visit whereas in the British population only half did so. This may suggest either that American patients are better informed about the significance of symptoms and what action to take or that British patients are more reticent and less inclined to "trouble the doctor." Nevertheless, it seems that a substantial proportion of patients already take action in response to symptoms during the follow up period.

The risk of relapse is maximal in the first two years after starting treatment (fig 2), which provides some basis for concentrating follow up effort during this period. Nevertheless, the absolute number of relapses is small (maximum 10 or 11 per 100 cases observed for one year), and in this study most were identified not as a result of routine screening of asymptomatic patients but by the appropriate investigation of symptoms when these occurred. Possibly a more intensive programme of surveillance (including interval computed tomography or gallium-67 scanning, for example) would lead to the earlier detection of relapse, but even if this was the case, benefit to patients would follow only if there was an associated survival advantage. Further studies are needed to address this issue and assess the degree of anxiety generated by or reassurance derived from a patient's visit to hospital for routine follow up.

In summary, our results suggest, firstly, that current follow up policy results in too many routine clinic

Key messages

- Follow up after treatment for Hodgkin's disease has several functions but detection of relapse is probably the most important
- In Hodgkin's disease the relapse rate is maximal 12-18 months after the start of treatment but declines rapidly thereafter
- Relapse is usually identified as a result of the investigation of symptoms rather than by routine screening of asymptomatic patients
- Routine clinic visits should be reduced in frequency and far greater emphasis placed on patient education; this should underline the importance of symptoms and encourage patients to arrange earlier appointments if these develop

visits; secondly, that relapse is usually diagnosed as a result of appropriate investigation of symptoms rather than by routine screening; and, thirdly, that at least some patients are prompted by symptoms to arrange an earlier appointment. A more rational strategy would be for routine visits to remain focused on the early years of follow up but to be reduced in overall frequency (we propose three monthly visits in year 1, four monthly visits in year 2, six monthly visits in year 3, and then yearly visits), coupled with far greater emphasis on patient education. This might include an information sheet to emphasise the importance of symptoms and encourage patients to arrange an earlier clinic appointment if they were, for example, to find a lump, lose weight, or develop a persistent cough or night sweats. We believe that such a policy would reduce the number of hospital visits but still provide sufficient opportunity for matters of concern to patients to be discussed and maximise the chances of early detection of relapse by encouraging patients to report new symptoms without delay.

The results of this study were presented at the 31st annual meeting of the American Society of Clinical Oncology, Los Angeles, 20-23 May 1995.

Funding: None.

Conflict of interest: None.

1 Radford JA, Crowther D, Rohatiner AZS, Ryder WDJ, Gupta RK, Oza A, *et al.* Results of a randomised trial comparing MVPP chemotherapy with a hybrid regimen, ChlVPP/EVA, in the initial treatment of Hodgkin's disease. *J Clin Oncol* 1995;13:2379-85.

2 Lister TA, Crowther D, Sutcliffe SB, Glatstein E, Cannellos GP, Young RC, *et al.* Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. *J Clin Oncol* 1989;7:1630-6.

3 Andersen PK, Borgan Ø, Gill RD, Keiding N. Smoothing the Nelson-Aalen estimator. In: *Statistical models based on counting processes.* New York: Springer-Verlag, 1993:229-55.

4 Weeks JC, Yeap BY, Canellos GP, Shipp MA. Value of follow-up procedures in patients with large-cell lymphoma who achieve a complete remission. *J Clin Oncol* 1991;9:1196-203.

(Accepted 29 November 1996)

Duplication of surgical research presentations

I C Cameron, J D Beard, M W R Reed

Department of Surgery, Royal Hallamshire Hospital, Sheffield S10 2JF

I C Cameron, *senior house officer in surgery*

M W R Reed, *consultant surgeon*

Northern General Hospital, Sheffield S5 7AU

J D Beard, *consultant vascular surgeon*

Correspondence to: Mr Reed.

BMJ 1997;314:346–7

Research often seems to be presented at more than one meeting. No studies of duplicate presentation of surgical research have been published, so we reviewed the published abstracts of presentations given at selected national meetings attended by general surgeons over 16 months.

Methods and results

We reviewed the abstracts of presentations given at meetings whose audiences were thought likely to overlap with the Association of Surgeons meeting (table 1). Papers from non-surgical departments, departments outside the United Kingdom and Ireland, and those updating multicentre trials were excluded. For each abstract the title, department, and first two authors were recorded. When the title or authors from the same department coincided the abstracts were read to detect duplication, defined as the methods being identical and the data identical or similar, including the addition of a few patients to a previous series.

We reviewed 1646 presentations, and included 945 in the study: 713 presentations were given once, 95 twice, 10 three times, and 3 four times. There were 821 original abstracts and 124 duplications, giving a duplication rate of 15%. The duplication rate from individual centres varied from 0 to 52%: eight produced no duplication, whereas three had rates over 40%. The duplication rate for meetings ranged from 7 to 48% (table 1). These results were circulated to the presidents of the societies for comment.

Comment

The 15% duplication rate we found may be an underestimate as some abstracts will have been presented before or after the study period: the highest duplication rates were at meetings in the middle of the

Table 1 Societies whose abstracts were reviewed and the duplication rate found

Society	Abstracts published	Date of meeting	Duplicate presentation rate (%)
British Association of Surgical Oncology	*European Journal of Surgical Oncology*	May 1993	48
		November 1993	36
Surgical Research Society	*British Journal of Surgery*	January 1993	15
		July 1993	27
		January 1994	30
Association of Surgeons of Great Britain and Ireland	—	April 1993	19
		April 1994	25
British Society of Gastroenterology	*Gut*	March 1993	16
		September 1993	20
		March 1994	14
British Transplant Society	*Transplant Proceedings*	April 1993	7
		October 1993	13
Vascular Surgical Society	*British Journal of Surgery*	November 1993	27
Nottingham Breast Meeting	*The Breast*	September 1993	24
British Association of Endocrine Surgeons Society	*British Journal of Surgery*	May 1993	9

study period. In deciding whether duplication is bad we must consider the reasons for research presentation. One reason is dissemination of new information: duplication would thus be justified at meetings where the audiences were different (such as the British Transplant Society or the Nottingham Breast Meeting, attended by many non-surgeons), a view supported by all the societies. The value of presentation in gleaning useful feedback is often cited, but unquantified.

The main reason for duplication is probably to embellish the authors' curriculum vitae. The reduction in the length of surgical training, with less time for research, may further pressurise trainees to duplicate presentations to bolster their curriculum vitae. One society supported the use of one national meeting as a rehearsal for another, but others thought this a waste of educational time for those hearing the work twice. The abstract acceptance rate at the meetings varies between 33% and 66% so duplication may deny other abstracts the opportunity of presentation. Many surgeons attend both a specialty meeting and the Association of Surgeons or Surgical Research Society, leading to considerable audience overlap. The Vascular Surgical Society in particular commented on the undesirable duplication of vascular research at its meeting and within a short time at the other two. Only the Surgical Research Society states that abstracts must not have been submitted elsewhere. The British Transplant Society inquires about previous submissions but does not automatically reject duplicates. Several societies were willing to introduce these questions to reduce duplication.

What else can be done? We suggest that research could be presented at regional meetings with subsequent presentation at a national specialty meeting or the Surgical Research Society. The prizewinning papers from these meetings could be re-presented at a plenary session of the Association of Surgeons to reach a wider audience. Closer cooperation between societies, with accepted abstracts being made available to other societies, possibly via a computerised database, and a timetable for abstract submission, would help detect and prevent duplication. The temptation to submit abstracts to multiple meetings in the hope of acceptance at one would thereby be avoided. The eradication of duplication may allow fewer meetings, increasing the opportunities for trainees to attend: this would be a more effective use of limited study leave.

All abstracts studied except those from the Association of Surgeons are published in journals (table 1). Duplicate publication of papers has been discouraged[1], but the duplicate publication of abstracts is as yet undebated.

Funding: None.
Conflict of interest: None.

1 Williamson RCN, Farndon JR, Murie JA, Johnson CD. Editors' announcement: dual publication/submission. *Br J Surg* 1993:80:681.

(Accepted 23 May 1996)

A randomised controlled trial of dictating the clinic letter in front of the patient

B W Lloyd

North Middlesex Hospital, London N18 1QX
B W Lloyd, *consultant paediatrician*

BMJ 1997;314:347–8

continued over

For some years I have dictated clinic letters to the referring general practitioner in the presence of the family. This was originally to avoid the difficulties of dictating the letter later, but I have come to believe that families appreciate the opportunity to hear what I am writing to the general practitioner. I decided to evaluate this.

Methods and results

One hundred consecutive, newly referred outpatients were included in the study provided that they spoke English well enough not to need a link worker. Patients were assigned to either the study group or the control group at the end of the consultation. The assignment was made according to which of two closely similar questionnaires (identical except for the last question) I drew from a randomly shuffled folder of questionnaires (box).

If a family was in the study group, I dictated my letter to the general practitioner in front of them. If the family was in the control group I dictated the letter after they had left the room.

Both groups were asked to fill out a questionnaire about "how we run the clinic" after leaving the consulting room. Its anonymity was emphasised. Apart from the last question of the questionnaire there was no clue that I was studying the way I dictated my letters. Data were analysed with χ^2 testing.

No significant differences were found between the levels of satisfaction of the two groups in terms of the perceived clarity of my explanation, the perceived usefulness of the consultation, or my perceived honesty (table 1). No parent used any rating less favourable than "well", "useful", or "honest."

All 50 study families indicated that they liked me dictating the letter to their general practitioner in front

Questionnaire given to parents participating in the study

1 How well did the doctor explain things?
Very well | Well | Not very well | Badly

2 How useful was the appointment?
Very useful | Useful | Not very useful | Useless

3 How honest do you think the doctor was with you?
Very honest | Honest | Not very honest | Dishonest

4 (If in study group) **Did you like the doctor dictating the letter to your GP in front of you?**
Yes | No | Don't know

5 (If in control group) **Would you have liked to hear the doctor dictating his letter about your child to your GP?**
Yes | No | Don't know

Correspondence to: Dr B W Lloyd, Children's Department, Royal Free Hospital, London NW3 2QG.

of them. Five control families indicated that they would not have liked to hear the letter, and 11 families did not know whether they would have liked to hear it or not. The other 34 control parents indicated that they would have liked to hear me dictate the letter.

Discussion

All parents who heard me dictate the letter reported that they liked hearing it dictated in front of them. Furthermore over two thirds of parents in the control group indicated that they would have liked to hear the letter dictated. Despite these findings, however, parents in the study group were no more satisfied with their consultations than those in the control group were.

I believe that what families like about the practice of dictating the letter in front of them is its openness. Further advantages include the opportunity for the parents to hear a formal summary of the consultation and the chance for them to correct the content of the letter. Letters written at the end of a consultation are likely to be more accurate and apt than letters written hours or days later. Partly because I write structured letters, few letters take more than two minutes to dictate.[1]

Table 1 Numbers of parents in the two groups (n = 50, both groups) who rated the doctor and the consultation in different ways

Parents' rating of doctor	Study group	Control group
Explained very well	37	42
Appointment very useful	45	36
Very honest	41	39

I have been unable to find any other studies of this matter. Rylance has shown that parents appreciate receiving tape recordings of outpatient consultations.[2] Practical considerations (including cost) may have stopped this practice becoming widespread. Like many other doctors[3 4] I now send copies of clinic letters to almost all families that I see for the first time. Nevertheless, I continue to dictate letters in front of the family, and this study has shown that they appreciate it.

1 Rawal J, Barnett P, Lloyd BW. Use of structured letters to improve communication between hospital doctors and general practitioners. *BMJ* 1993;307:1044.
2 Rylance G. Should audio recordings of outpatient consultations be presented to patients? *Arch Dis Child* 1992;67:622-4.
3 Tattersall R. Writing for and to patients. *Diabet Med* 1990;7:917-9.
4 Damian D, Tattersall MHN. Letters to patients: improving communication in cancer care. *Lancet* 1991;338:923-5.

(Accepted 26 September 1996)

Commentary: Interesting idea, but case not proved

Mike Pringle

Department of General Practice, Medical School, Queen's Medical Centre, Nottingham NG7 2UH

Mike Pringle, *professor of general practice*

B W Lloyd has produced a paper of interest and originality. If his evidence were compelling—or indeed if it were confirmed by others in a more rigorous study—then a small but important behavioural shift in doctor behaviour might follow. A more open consultation in which the patient feels respected as a full partner may benefit both parties. All my intuition (and my personal experience, for I too dictate many letters in front of patients) tells me that his conclusions are right. But intuition is clearly insufficient evidence especially in such an emotive area.

Before I can be persuaded of Lloyd's conclusions I must firstly know much more about his study. There is implicit evidence that the setting was a paediatric clinic, but were the respondents to the questionnaires the patients, their parents, both, or a mixture? Were these consultations first attendances or follow ups, and if both, was the ratio the same in both groups?

Perhaps the most important missing data relate to the case mix. Dictating a letter about asthma in front of the child and parents might be thought to be a low risk activity, but there are serious potential implications when the child has a new diagnosis of, say, leukaemia. If the lessons from this article are to be generalised, we need to know whether the general practice equivalent is dictating an antenatal referral letter in front of a newly pregnant woman, or dictating a letter to a psychiatrist. Indeed, no one is likely to advocate blanket policy of dictation in front of all patients; a selective approach would always be sensible.

The second area that needs clarification, and further study, is the sensitivity of the research tool used. Only one pair of questions ("Did you like the doctor dictating the letter to the GP in front of you?" versus "Would you have liked to hear the doctor dictating his letter about your child to your GP?") produced a difference between the two groups. However, one group is commenting on an experience received, while the other is speculating on an experience the nature of which it can only guess. It would have been astounding if such a loaded question did not yield a "positive" response.

The other questions show a lack of awareness of the science of patient satisfaction. That all the respondents used only two of the four response categories shows that the survey was never likely to be a sensitive tool in this context. The use of tools validated in similar circumstances[1-4] would be more likely to yield comparable and valid findings.

It has to be acknowledged, however, that in a brief and provocative study Lloyd has posed a question that should stimulate others to explore this issue in greater depth; and that is presumably the challenge that the *BMJ*, by publishing this paper, is laying down to those of us interested in researching the consultation.

1 Bruster S, Jarman B, Bosanquet N, Weston D, Erens R, Delbranco T. National survey of hospital patients. *BMJ* 1994;309:1542-9.
2 Campbell M, Sullivan F, Murray TS. Videotaping of general practice consultations: effects on patient satisfaction. *BMJ* 1995;311:236.
3 Poulton B. Use of consultation satisfaction questionnaire to examine patients' satisfaction with general practitioners and community nurses: reliability, replicability and discriminant validity. *Br J Gen Pract* 1995;46:26-31.
4 Kinnersley P, Stott N, Peters T, Harvey I, Hackett P. A comparison of methods for measuring patient satisfaction with consultations in primary care. *Family Practice* 1996;13:41-51.