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Surveillance of antibody to measles, mumps, and rubella by age

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Abstract

Before the introduction of measles, mumps, and rubella vaccine a survey was carried out to measure antibody prevalence to the three viruses by age. A total of 8716 samples of serum collected by five public health laboratories in different parts of England during 1986-7 were tested. Despite the current measles vaccination programme 60% of children aged 1-2 years did not have measles antibody and over 80% did not have antibodies to mumps and rubella. In the 3-4 year age group 17% of the children were susceptible to measles, 55% to mumps, and 73% to rubella. The results suggest that vaccinating children early in the second year of life will be necessary to eliminate the three diseases.

The survey provides baseline data for continuing surveillance of the immediate and long term effects of the new vaccination strategy.

Introduction

Development of effective strategies of vaccination and assessment of their impact require knowledge of the prevalence of antibody by age for the diseases concerned. Preceding the introduction of measles, mumps, and rubella vaccine, a study of antibody prevalence to measles, mumps, and rubella viruses across the age range 1-65 years and over has been carried out. This has provided information on the most suitable age for vaccination and baseline data on antibody prevalence as part of continuous surveillance to monitor both immediate and long term effects of introducing the vaccine.

Subjects and methods

In five public health laboratories (Ashford, Bristol, Leeds, Manchester, and Preston) serum remaining from samples submitted for routine diagnostic examination was saved from patients aged 1-65 years and over. Samples from immunocompromised patients and samples sent for testing for antibody to hepatitis B and the human immunodeficiency virus were excluded.

The serum samples were tested for rubella antibody by radial haemolysis[1] in each laboratory. Samples giving zone sizes greater than that of a control serum containing 15 IU rubella antibody were recorded as positive and those with no zone as negative. Samples giving small zones compared with the control serum or zones on both test and control gels were retested at Preston Public Health Laboratory by latex agglutination (Orion Diagnostica, Espoo, Finland) and recorded as positive or negative accordingly. Samples were tested for measles and mumps antibodies at Preston Public Health Laboratory. Mumps antibody was detected by radial haemolysis.[2] A serum (arbitrarily assigned as having 50 units of antibody) from a person who had had mumps in the remote past was diluted in negative serum. At a dilution of one in 10 (5 antibody units) antibody was reproducibly detected by radial haemolysis during preliminary evaluation, and this dilution was tested on every gel. Test samples giving zones of haemolysis greater than that of the diluted standard were considered to be positive and those giving no zone negative. Samples giving zones on test and control gels were retested after absorption with day old chick red cells and non-infected allantoic fluid. Samples giving zones less than that of the diluted standard were retested with a commercial antiglobulin enzyme linked immunosorbent assay (ELISA) (Behringwerke AG, Marburg, West Germany) and classified according to result. Measles antibody was detected by haemagglutination inhibition.[3] Serum samples were compared with a serum standardised against the first British standard human antimeasles serum and samples with a concentration equal to or greater than 0·3 IU (usually a titre of 8 by haemagglutination inhibition) were considered to be positive, and those with a concentration below 0·15 IU negative. Samples with a concentration of 0·15 IU were retested with a commercial antiglobulin ELISA and assigned as positive or negative according to the result

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obtained. Final results were analysed at the Communicable Disease Surveillance Centre.

Results

Results were obtained for 8716 serum samples taken between November 1986 and December 1987. An average of 250 samples were tested for each year of age from 1-14, two years of age from 15-34, five years from 35-44, and 10 years thereafter. There were no consistent differences among laboratories in the proportions of subjects who were susceptible to measles, mumps, and rubella at different ages. The results from all five laboratories have therefore been summed (table I).

TABLE I—*Number (percentage) of serum samples negative for antibody to measles, mumps, and rubella by age*

Age (years)	No of samples	Measles	Mumps	Rubella
1- <2	398	237 (60)	354 (89)	347 (87)
2- <3	290	86 (30)	248 (86)	239 (82)
3- <4	324	60 (19)	200 (62)	260 (80)
4- <5	365	56 (15)	136 (37)	244 (67)
5- 9	1474	138 (9)	336 (24)	647 (44)
10- 12	876	45 (5)	118 (13)	184 (12)
13- 16	903	42 (5)	105 (12)	111 (12)
17- 30	2366	117 (5)	208 (9)	174 (7)
31-≥65	1720	66 (4)	172 (10)	124 (7)

Sixty per cent of children in the second year of life did not have measles antibody, the proportion decreasing to 30% during the third year. In contrast, over 80% of children of the same age did not have antibodies to mumps and rubella. Susceptibility to mumps declined sharply in the 3-<5 age group; that to rubella declined later. After the age of 12 there was no significant downward trend in the proportions of subjects who did not have measles or mumps antibody.

As shown in table II, the proportions of subjects who did not have rubella antibody were significantly lower in females than in males in age groups between 10 and 30 ($p<0.01$), reflecting the effect of selective rubella vaccination of girls and women. Susceptibility in women too old to have been offered rubella vaccine at school (31 and over) was higher than in younger women and not significantly different from that in men of the same age. There was no significant difference between the sexes in the proportions without antibody to either measles or mumps at any age.

TABLE II—*Serum samples negative for antibody to rubella by age and sex*

	Male		Female	
Age (years)	No of samples	No (%)	No of samples	No (%)
1- 2	343	295 (86)	345	291 (84)
3- 4	350	265 (76)	339	239 (71)
5- 9	826	371 (45)	648	276 (43)
10- 12	468	121 (26)	408	63 (15)
13- 16	454	96 (21)	449	15 (3)
17- 30	1183	130 (11)	1183	44 (4)
31-≥65	859	66 (8)	861	58 (7)

Discussion

This is the largest survey of the prevalence of antibodies to measles, mumps, and rubella viruses across the whole age range to be reported in the United Kingdom. The subjects tested were not randomly sampled from the population as this is not feasible for ethical, practical, and financial reasons. Each laboratory in the study, however, serves a large and fairly constant catchment area; by using the same laboratories in repeat surveys future changes in the prevalence of antibody by age in these populations should become apparent. During 1988 other laboratories, including one in London, have been included in the surveillance. The assays used for detecting antibodies to measles, mumps, and rubella are well established and appropriate for testing large numbers of serum samples. The use of standard control serum will ensure comparability with results in future years.

The lower proportion of children aged 1-<3 susceptible to measles compared with mumps and rubella reflects the current uptake of measles vaccine of around 70% by the end of the second year of life.[4] The decline in susceptibility to measles in children aged 3-5 is more probably due to infection than to vaccination at this age, as a yearly average of 40 000 cases have been notified in children under 5 in the past few years.[5] The data show that mumps is also predominantly a preschool infection as by the age of 5 only 33% of children are still susceptible. Clearly, to control the circulation of measles and mumps vaccination early in the second year of life is important. Though the data show that rubella is acquired later than measles and mumps, maximum effect will still be achieved by early vaccination.

During the first few years of the programme measles, mumps, and rubella vaccine will also be offered to all children aged 4-5 to reduce the number of susceptible children entering school and thereby limit the spread of infection in the primary school population. This should be particularly valuable for rubella as the data show that two thirds of children are still susceptible when they enter school. For practical reasons the main target of the "catch up" programme will be children attending for their preschool diphtheria and tetanus booster, but in addition no opportunity should be missed to vaccinate children aged 2-4. In future years vaccination of preschool children should apply only to those whose measles, mumps, and rubella vaccination has been missed. It should not be regarded as an alternative opportunity, as delaying immunisation to this age will inevitably allow continuing circulation of the viruses in the preschool population. This has been observed in the United States, where laws on school entry ensure a high uptake at that age, but where outbreaks of measles continue in preschool children.[6]

A two stage vaccination policy at 1-2 years of age and again at 12, adopted in Sweden,[7] would not be justified here at present because of the fairly small proportion of children currently susceptible in the older age group. If future surveillance, however, shows an increase in the proportions of older children who do not have antibodies a two stage vaccination programme might become appropriate.

Susceptibility to measles and mumps did not decline significantly after 12. With rubella, however, there is some evidence that antibody titres decline with age,[8] and some of the older subjects in our study who were categorised as having no rubella antibody might have antibody detected by alternative techniques. Serum samples that were negative on the initial screening have not so far been retested. Mass vaccination will inevitably have a profound effect on the epidemiology of measles, mumps, and rubella. The immediate effect should be an increase in prevalence of antibodies in the vaccinated cohorts. In the long term, however, indirect effects may occur in the older age groups, in which reduced exposure to disease could result in increased susceptibility, thereby allowing the continued circulation of the viruses. The serological surveillance described, together with the monitoring of the incidence of disease and uptake of the vaccine will allow such susceptible cohorts to be identified and the necessary action taken to eliminate measles, mumps, and rubella.

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Sclerosis of lytic bone metastases after disodium aminohydroxypropylidene bisphosphonate (APD) in patients with breast carcinoma

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Bisphosphonates, which are potent inhibitors of osteoclast function, reduce morbidity from bone metastases when used with systemic chemotherapy.[1] The contribution of each treatment in any patient is not known. We assessed the effect of disodium aminohydroxypropylidene bisphosphonate (APD) used either alone or in patients receiving endocrine treatment whose disease was progressing.

Patients, methods, and results

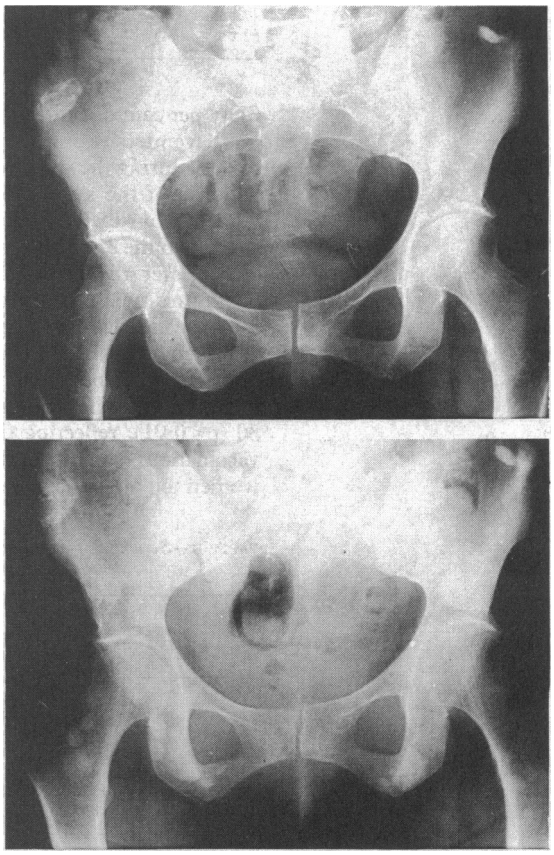
We studied 16 patients with breast carcinoma who had progressing metastases in bone for six months or until their disease progressed again despite treatment. APD (Ciba-Geigy) was administered intravenously (30 mg in 500 ml of 0·9% saline over two hours) weekly for four weeks and thereafter fortnightly. At each visit we measured serum calcium, albumin, and phosphate concentrations; alkaline phosphatase activity; and ratios of fasting urinary calcium to creatinine and hydroxyproline to creatinine concentrations. Serum concentrations of osteocalcin and tumour markers (carcinoembryonic antigen and carbohydrate antigen 15:3[2]) were measured monthly. Pain was scored on a linear analogue scale and the Karnofsky performance state assessed at each visit. A baseline isotope bone scan and plain radiographs of the chest, thoracolumbar spine, and pelvis were obtained. Radiography was repeated every six weeks. Evidence of sclerosis in a previously lytic lesion in the absence of new lesions was taken as a response to treatment. Statistical analysis was by Friedman's non-parametric two way analysis of variance.

Patients tolerated the infusions of APD well. Eight patients were withdrawn within six months with evidence of progressing disease (three in bone, five at other sites).

Effect on symptoms—Patients' perception of their pain, expressed as a percentage on the linear analogue scale, decreased significantly ($p<0·01$) from a median of 69% (range 42-90%) to 32% (5-75%) but was unrelated to radiological response. The Karnofsky performance state improved from a median of 70 (range 50-80) to 80 (60-90) ($p<0·025$).

Effects on biochemical variables—No significant change in serum calcium or phosphate concentrations occurred. The molar ratio of urinary calcium to creatinine concentrations fell significantly from a median of 0·63 (range 0·10-1·38) to 0·12 (0·02-0·67) ($p<0·001$) after the first infusion of APD. Patients who showed radiological improvement tended to have particularly low urinary ratios. The ratio rose dramatically in three patients whose disease progressed in bone. No significant change in alkaline phosphatase activity, osteocalcin concentration, or ratio of urinary hydroxyproline to creatinine concentrations was seen.

Antitumour effect—At six months radiological evidence of sclerosis of lytic metastases (figure) was seen in four patients and no change in the other four.



Lytic bone metastases before (top) and after (bottom) treatment with APD

Concentrations of both carcinoembryonic antigen and carbohydrate antigen 15:3 fell in three patients (two who had a partial response and one whose disease remained stable), remained unchanged in eight patients, and rose in five.

Comment

APD produced sclerosis of lytic metastases in four patients, and in four others the disease remained stable by radiological criteria over six months. Patients who responded to APD seemed to show greatest suppression of bone resorption as reflected in their low ratios of urinary calcium to creatinine concentrations. Tumour marker concentrations fell in three of the