PAPERS AND SHORT REPORTS

Rubella vaccination: persistence of antibodies for up to 16 years

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Abstract

Sera from 123 volunteers vaccinated six to 16 years previously with one of four rubella vaccines (Cendehill, RA27/3, HPV77-DE5, and To-336) were tested for rubella antibodies by single radial haemolysis and radioimmunoassay. By radioimmunoassay 110 (89·4%) of the vaccinees had antibody concentrations greater than the minimum immune titre (that is, >15 000 IU/l), 11 (8·9%) were seropositive but had concentrations ≤15 000 IU/l, and two (1·6%) were seronegative. Eight (6·5%) were seronegative by single radial haemolysis, of whom five had received Cendehill vaccine. Six to eight years after vaccination subjects who had received Cendehill vaccine had the lowest geometric mean titre of antibody by radioimmunoassay while the subjects who had received HPV77-DE5 vaccine had the highest. Although antibody concentrations ≤15 000 IU/l were not detected among subjects given RA27/3 vaccine six to eight years previously, such low levels were detected in two (15·4%) vaccinated 11-16 years previously.

These results emphasise the importance of long-term surveillance programmes so that vaccination policies may be reviewed.

Introduction

Rubella vaccines, which make congenitally acquired rubella a preventable disease, have been licensed for over a decade in the United Kingdom and United States. Elimination of congenitally acquired infection depends not only on adequate uptake of vaccine, however, but also on the persistence of antibody throughout childbearing years. Thus adequate antibody concentrations must persist for at least 30 years after vaccination of 11- to 14-year-old schoolgirls in the UK and for even longer in the US, where most children are vaccinated before entering school. Some concern was expressed in the US over reports from Horstmann[1] and Balfour and Amren[2] that 8·5% and 36% of children respectively no longer had detectable haemagglutination-inhibiting antibody three to nine years after vaccination with HPV77-DE5 (Meruvax-1) vaccine. As a result of these findings the need for revaccination was discussed.[3] More recently, however, Herrmann *et al*[4] reported loss of antibody in less than 3% of children vaccinated with HPV77-DE5 vaccine 10 years previously. Recent studies in the UK[5] have also been encouraging, showing that over 90% of subjects who received RA27/3 (Almevax) or Cendehill (Cendevax) vaccines six to seven years previously had adequate antibody titres. Similarly, studies in the Irish Republic have shown persistence of antibody for up to 10 years after vaccination with RA27/3 vaccine.[6]

We report a study in which we tested sera obtained in 1981 from adult female volunteers vaccinated up to 16 years previously with one of four rubella vaccines. Some of these women were among the earliest rubella vaccinees in the UK, and these sera therefore represent a unique collection. Earlier studies generally used only titres of haemagglutination-inhibiting antibody to assess persistence of rubella antibodies. In this study sera were tested by single radial haemolysis and radioimmunoassay, both of which are more sensitive than tests for haemagglutination-inhibiting antibody, particularly in detecting low levels of antibody.[7]

Subjects and methods

We studied two groups of volunteers. The first had been vaccinated with RA27/3, Cendehill, HPV77-DE5, or a Japanese vaccine, To-336, six to eight years previously while medical students or student nurses at St Thomas's Hospital.[8] Nine volunteers who had experienced natural infection at about the same time were also followed up. The second group of 38 volunteers had received either RA27/3 or Cendehill vaccine, in 12 cases 14 to 16 years previously and in 26 cases 11-13 years previously, while student nurses at the Hospital for Sick Children, London.[9] All volunteers had been seronegative (titre of

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haemagglutination-inhibiting antibody < 4) before vaccination and had seroconverted (antibody titre >8) six to eight weeks after vaccination.

Sera obtained in 1981 were tested for rubella antibodies by single radial haemolysis[10] and for rubella-specific IgG by radioimmunoassay.[11] By single radial haemolysis zones of haemolysis were compared with that of the standard minimum immune titre serum, which contains 15 000 IU rubella antibody/l[10] and was supplied by the Central Public Health Laboratory, Colindale. Sera were classified as seropositive (zone >15 000 IU/l), low titre (zone ≤15 000 IU/l), or seronegative (no zone). Fourfold dilutions of sera were tested by radioimmunoassay; the minimum immune titre serum had a titre of 160 in this test. Tests of significance were carried out using unpaired *t* tests.

Results

Low concentrations of antibody (≤15 000 IU/l) were detected in 19 of the 123 (15·4%) vaccinees by single radial haemolysis and in 13 (10·6%) by radioimmunoassay (table I). Antibody concentrations ≤15 000 IU/l occurred more frequently among subjects given Cendehill vaccine. None of those with naturally acquired immunity had antibody concentrations ≤15 000 IU/l. Antibody concentrations ≤15 000 IU/l occurred more commonly among those vaccinated 11 to 16 years previously than among those vaccinated six to eight years previously.

Eight of the 123 (6·5%) vaccinees had no detectable antibody when tested by single radial haemolysis (table I); five of these eight had been given the Cendehill vaccine. When tested by radioimmunoassay, however, only two of the 123 (1·6%) were seronegative. Only one vaccinee who had been given RA27/3 vaccine was negative by radioimmunoassay although she had a low concentration of antibody (<15 000 IU/l) when tested by single radial haemolysis. This girl had been vaccinated 11 years previously.

Table II shows the geometric mean titres of rubella-specific IgG by radioimmunoassay. Titres were significantly higher after naturally acquired infection than vaccination (t_{130} value = 3·12, $p < 0·005$). Among volunteers vaccinated six to eight years previously RA27/3 and HPV77-DE5 induced the highest geometric mean titres and Cendehill the lowest. In contrast, volunteers vaccinated 11 to 16 years previously with RA27/3 vaccine had a lower geometric mean titre (465) than those given Cendehill (821), but this difference was not significant (t_{36} value = 1·30, $p = 0·2$). Volunteers who had received RA27/3 vaccine 11-16 years previously had a significantly lower geometric mean titre than those vaccinated only six to eight years previously (t_{44} value = 2·05, $p < 0·005$). In contrast, volunteers given Cendehill 11-16 years previously had a higher geometric mean titre (821) than those given the vaccine six to eight years previously (355), but this difference was not significant (t_{43} value = 1·96, $p > 0·05$).

TABLE I—*Results of assays in volunteers from St Thomas's Hospital vaccinated six to eight years previously* and from the Hospital for Sick Children vaccinated 11-16 years previously*

Vaccine received	No of subjects	No (%) seronegative		No (%) with antibodies ≤15 000 IU/l	
		Single radial haemolysis	Radioimmunoassay	Single radial haemolysis	Radioimmunoassay
All subjects (n = 123)					
RA27/3	46	0	1 (2·2)	3 (6·5)	2 (4·3)
Cendehill	45	5 (11·1)	1 (2·2)	12 (26·7)	8 (17·8)
HPV77-DE5	18	2 (11·1)	0	3 (16·7)	2 (11·1)
To-336	14	1 (7·1)	0	1 (7·1)	1 (7·1)
Total	123	8 (6·5)	2 (1·6)	19 (15·4)	13 (10·6)
*Volunteers from St Thomas's Hospital (n = 85)**					
RA27/3	33	0	0	0	0
Cendehill	20	2 (10·0)	1 (5·0)	6 (30·0)	6 (30·0)
HPV77-DE5	18	2 (11·1)	0	3 (16·7)	2 (11·1)
To-336	14	1 (7·1)	0	1 (7·1)	1 (7·1)
Total	85	5 (5·9)	1 (1·2)	10 (11·8)	9 (10·6)
Volunteers from Hospital for Sick Children (n = 38)					
RA27/3	13	0	1 (7·7)	3 (23·1)	2 (15·4)
Cendehill	25	3 (12·0)	0	6 (24·0)	2 (8·0)
Total	38	3 (7·9)	1 (2·6)	9 (23·7)	4 (10·5)

*Nine additional subjects from St Thomas's Hospital who had acquired natural infection at about the same time were also followed up: none were seronegative or had antibody concentrations ≤15 000 IU/l.

TABLE II—*Geometric mean antibody titres and ranges as measured by radioimmunoassay in volunteers who had experienced naturally acquired infection or had been vaccinated six to eight years previously at St Thomas's Hospital and 11-16 years previously at the Hospital for Sick Children*

Vaccine received	No of subjects	Antibody titres	
		Range	Geometric mean
Subjects who had acquired natural infection (n = 9)			
None	9	1280-5120	2764
All vaccinees (n = 123)			
RA27/3	46	<20-5120	652
HPV77-DE5	18	80-5120	1185
To-336	14	80-5120	780
Cendehill	45	<20-5120	540
Total	123	<20-5120	755·2
Vaccinees from St Thomas's Hospital (n = 85)			
RA27/3	33	320-5120	915
HPV77-DE5	18	80-5120	1185
To-336	14	80-5120	780
Cendehill	20	<20-5120	355
Total	85	<20-5120	740
Vaccinees from Hospital for Sick Children (n = 38)			
RA27/3	13	<20-1280	465
Cendehill	25	80-5120	821
Total	38	<20-5120	617·6

Discussion

It is encouraging that we could detect antibody in over 90% of volunteers vaccinated up to 16 years previously. Although, overall, the results with RA27/3 were encouraging, differences were apparent in antibody responses of volunteers vaccinated six to eight years previously compared with those who had received the vaccine between 11 and 16 years previously. This might be important since not only is RA27/3 one of the two vaccines licensed in the UK but it is now the only vaccine currently available in the US. Although the number of sera tested, particularly 11 to 16 years after vaccination, was fairly small, this difference may reflect a decrease of RA27/3-induced antibodies with time. Alternatively, it might be argued that differences in the potency of vaccine batches in the earlier trials may have been responsible, since these batches were among the first to be used for clinical trials in this country.[12]

Loss of detectable antibody, which created anxiety in the US, was not so apparent in our study, even in those given HP77-DE5. Our numbers were smaller, however, and adults rather than children were vaccinated.

We previously showed that Cendehill induces not only lower antibody concentrations than RA27/3 but also a less durable local antibody response.[13] Furthermore, on intranasal challenge with RA27/3, reinfection, as measured by boost in antibody titres and production of rubella-specific IgM, occurred more commonly in subjects given Cendehill vaccine.[14] MacDonald *et al*[15] also showed a higher incidence of naturally acquired reinfection in subjects given Cendehill vaccine. Such booster antibody responses might account for the higher geometric mean titres in the volunteers given Cendehill vaccine 11-16 years previously compared with those who had received the vaccine six to eight years previously.

By both single radial haemolysis and radioimmunoassay 11 (8·9%) of the vaccinees in our study had antibodies, but ≤15 000 IU/l. Whether such low concentrations are protective and will prevent viraemia after exposure to natural infections remains to be determined. We recently reported two cases of viraemia in women who had low concentrations of antibody (<15 000 IU/l) before challenge with RA27/3.[16,17] It is important that further long-term surveillance be continued over 30-40 years so that vaccination policies may be reviewed and revaccination considered if an appreciable number of vaccinees lose detectable antibody within this time. Such studies should also be supported by challenge of individuals with low or

undetectable antibody concentrations to determine whether they are protected.

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Requests for reprints should be sent to JEB.

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Indium-111 autologous leucocyte scanning: comparison with radiology for imaging the colon in inflammatory bowel disease

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Abstract

Indium-111 autologous leucocyte scanning was compared with barium enema for assessing the extent of colonic disease in Crohn's colitis and ulcerative colitis. Scanning was shown to be as accurate as conventional radiology in colitis, reliably distinguishing active from inactive disease.

The results suggest that ^{111}In-leucocyte scanning is an accurate, non-invasive, alternative technique for imaging the extent of disease in colitis.

Introduction

A rapid and effective isotopic method of visualising inflamed bowel might offer advantages over conventional radiological techniques in medical and surgical gastroenterology. Initial promising results with ^{99m}Tc-diethylenetriamine penta-acetic acid could not be repeated in later studies.[1 2] Though ^{67}Ga-citrate has been used successfully in ulcerative colitis,[3 4] its value appears to be both limited[4] and unpredictable[5] in Crohn's disease. Indium-111-labelled leucocyte scanning is now established as an effective method of locating sepsis,[6-9] and in preliminary studies we and others have shown that it can image inflamed bowel.[10 11] We have therefore examined the imaging potential of ^{111}In-leucocyte scanning in ulcerative colitis and Crohn's colitis as compared with radiology.

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Patients and methods

We studied 20 patients with colitis (see table). In all cases the diagnosis was confirmed histologically. Spread to the small bowel in patients with Crohn's disease was excluded by barium follow-through. From clinical and histological assessment, 17 patients had active colitis and three inactive disease. Colonoscopy was available within two weeks of the scan in six patients (three with active and all three with inactive disease). Nine patients were receiving treatment in the form of steroids or sulphasalazine at the time of the scan.

Radiology—Double-contrast barium enema was performed in 19 patients. The remaining patient was considered too ill for the procedure and the extent of disease was assessed by late barium follow-through films and confirmed by surgery. The extent of colitis was assessed by the radiologist performing the barium study (who was unaware of the result of the leucocyte scan) and classified according to regional disease, regions 1, 2, and 3 corresponding to descending, transverse, and ascending colon, respectively. Radiology was performed within two weeks of the leucocyte scan in 17 patients. In the remaining three barium enema was performed three to four months before the scan.

Scanning—Leucocytes were labelled either in saline with ^{111}In-acetylacetonate (eight patients)[12] or in plasma with ^{111}In-tropolonate (12 patients).[13] Abdominal scans were performed within four