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Chapter 3

Immunogenicity of second dose measles-mumps-rubella vaccine and implications for serosurveillance

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Immunogenicity of second dose measles–mumps–rubella (MMR) vaccine and implications for serosurveillance

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Abstract

Measles and mumps, but not rubella, outbreaks have been reported amongst populations highly vaccinated with a single dose of measles–mumps–rubella (MMR) vaccine. Repeated experience has shown that a two-dose regime of measles vaccine is required to eliminate measles. This paper reports the effect of the first and second MMR doses on specific antibody levels in a variety of populations.

2–4 years after receiving a first dose of MMR vaccine at age 12–18 months, it was found that a large proportion of pre-school children had measles (19.5%) and mumps (23.4%) IgG antibody below the putative level of protection. Only a small proportion (4.6%) had rubella antibody below the putative protective level. A total of 41% had negative or equivocal levels to one or more antigens. The proportion measles antibody negative (but not rubella or mumps) was significantly higher in children vaccinated at 12 months of age than at 13–17 months. There was no evidence for correlation of seropositivity to each antigen, other than that produced by a small excess of children (1%) negative to all three antigens. After a second dose of MMR, the proportion negative to one or more antigens dropped to <4%. Examination of national serosurveillance data, found that following an MR vaccine campaign in cohorts that previously received MMR, both measles and rubella antibody levels were initially boosted but declined to pre-vaccination levels within 3 years.

Our study supports the policy of administering a second dose of MMR vaccine to all children. However, continued monitoring of long-term population protection will be required and this study suggests that in highly vaccinated populations, total measles (and rubella) IgG antibody levels may not be an accurate reflection of protection. Further studies including qualitative measures, such as avidity, in different populations are merited and may contribute to the understanding of MMR population protection. © 2002 Elsevier Science Ltd. All rights reserved.

Keywords: Rubella; Measles; Mumps

1. Introduction

Measles outbreaks in cohorts highly vaccinated with a single dose of MMR vaccine have been frequently reported, mumps outbreaks occasionally and rubella never [1–5]. Reduced vaccine effectiveness has been explained as due either to primary (PVF) or secondary vaccine failure (SVF). PVF represents a failure of immediate seroconversion with a documented lack of detectable-specific antibody. Administration of a second dose of vaccine to primary vaccine failures results in a high proportion undergoing a primary antibody response, with an initial IgM response followed by IgG seroconversion. SVF is infection in an individual following initial documented seroconversion, and represents a loss of protection, often linked to waning serum antibody levels [6]. Following a second dose of vaccine, a large boost in IgG antibody levels generally occurs, with little or no IgM response. In the case of measles, although specific concentrations of IgG antibody have been postulated as protective thresholds against clinical disease [7], a graduated relationship between IgG level and degree of protection may be more likely.

For mumps vaccine, vaccine failure rates vary depending on the vaccine strain. PVF plays an important role, but the relative contribution of SVF is unclear [1,5,8,9]. For measles vaccine, the situation following a single vaccine dose is also unclear [9–13]. Clinical disease amongst vaccinated individuals exposed to wild measles virus is milder or asymptomatic compared to unvaccinated individuals [14,15] and suggests a role for SVF. However, the epidemiological significance of waning population immunity in relation to sustained transmission remains uncertain [16].

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Despite high first dose coverage, most countries in North America and Western Europe have introduced a routine second dose of MMR vaccine, to overcome the problems of vaccine failure [17,18]. In the UK, single dose MMR replaced single antigen measles at 12–15 months of age in 1988. In 1994, a national campaign vaccinated 92% of 5–16 years old with MR vaccine, to prevent a predicted measles epidemic [19]. In October 1996, a second, pre-school MMR dose was added to the immunisation programme. These changes resulted in a low reported incidence of measles, mumps and rubella in the UK in the 1990s.

This paper reports the effect of measles, mumps and rubella vaccination on specific antibody levels in a variety of populations of children in whom there has been little opportunity for natural boosting. The paper specifically explores the type and level of antibody response following the first and second dose of MMR vaccine and discusses the implications for immunisation strategy.

2. Methods

Serological data were acquired from two sources: a vaccine trial (for acellular pertussis vaccine in pre-school children [20]) and from the national serological surveillance programme in England and Wales [22].

2.1. Pre-school booster trial (PSB) for DTaP and MMR

This trial was a phase 2 acellular DTP (DTaP) vaccine booster trial in a population of pre-school children. Details of the double-blind randomised study design, population and ethical approval are reported elsewhere [20]. Due to the introduction in the national vaccination programme of a second dose of MMR midway, there was an opportunity to measure the measles, mumps and rubella IgM and IgG levels in populations who had not received a second dose.

The PSB study recruited a total of 1033 children aged 3.5–6 years between 1995 and 1997. Of these a sample of 610 eligible children were selected between September 1995 and October 1997. All had received a first dose of MMR. Before October 1992, three MMR vaccines were used: Pluserix (SmithKline Beecham, containing Schwarz measles strain, RA 27/3 rubella, Urabe-9 mumps strain); MMR II (Merck Sharp Dohme, containing Enders' Edmonston measles strain, RA 27/3 rubella, Jeryl Lynn mumps) and Immravax (Merieux, containing Schwarz measles strain, RA 27/3 rubella, Urabe-9 mumps strain). After 1992, only the MMR II vaccine was used. Children recruited to the study after October 1996 were offered a second dose of MMR II, although this was not a condition for enrolment. The vaccines were administered simultaneously by the study nurses by intramuscular injection in the arm, leg or buttock. MMR was administered at a different injection site to the DTaP or DT vaccine. Venous blood samples were collected from each child 4–6 weeks after the second MMR dose.

A total of 389 (63.7%) children were bled 4 weeks after receiving only a pre-school acellular DTP or just DT booster, and 221 (36.3%), 4 weeks after receiving a pre-school DTP/DT booster and MMR second dose. The sex distribution of the two groups was balanced (one dose group 48% female, two dose group 50% female, $P = 0.65$).

2.2. Serological surveillance data for rubella and measles

The PHLS serological surveillance programme involves the annual collection of residual sera from 18 public health laboratories throughout England and Wales. These are tested for a variety of antibodies including to measles, mumps and rubella. The sera are anonymised, only retaining information on age, sex and collecting laboratory [21].

The surveillance data were analysed to examine the second dose effect of the 1994 MR campaign on the 1988 and 1989 birth cohorts for the 4 years between 1994 and 1997. These birth cohorts would have been scheduled for a single dose of MMR vaccine at age 12–18 months, and to receive MR vaccine in the campaign in November 1994. The 1995–1997 results thus represent antibody levels in the 3 years after this second dose. For the 1988 birth cohort 96, 93, 90 and 103 sera were tested for the years 1994–1997, respectively, with 95, 92, 90 and 109 sera, respectively from the 1989 cohort.

2.2.1. Laboratory methods

Serum specimens from both trials and from the national serosurveillance programme were separated, stored at −30 °C and transported frozen to Preston Public Health Laboratory where they were tested for IgG antibody specific for measles, mumps and rubella.

Commercial enzyme immunoassays were used. For measles, an ELISA kit (Gull Ltd.; distributed by Launch Diagnostics, catalogue number RGE-100) was used, including the Second British standard (diluted in PBS) as control serum. Quantitative IgG results were classified as positive, equivocal or negative according to the concentrations: ≥100 mIU/ml positive, 50–99 mIU/ml equivocal, and 0–49 mIU/ml negative.

For mumps, an ELISA kit (Human Ltd., Germany; UK distributor Biostat Ltd., catalogue number 851207) was used together with an in-house standard developed as part of the European Seroepidemiology Network project (ESEN) [23]. Quantitative IgG results were classified according to the kit cut-offs.

For rubella, an ELISA kit (Trinity Biotech, Eire; UK distributor Microgen Ltd., catalogue number 801–335) was used together with the WHO standard (diluted in PBS) as control serum. Quantitative IgG results were classified as positive, equivocal or negative according to the following concentrations: ≥10 IU/ml positive; 5–9 IU/ml equivocal and 0–4 IU/ml negative.

For the PSB study, sera were also sent to the Central Public Health Laboratory, London to be tested for IgM antibody specific for measles, mumps and rubella antibody-capture radioimmunoassay (MACRIA) was used as previously described [23]. IgM antibody positivity was defined as a test/negative (T/N) ratio >2.5 for rubella and measles and 3.0 for mumps. Repeat testing of all positives was undertaken by the same method. Sera were reclassified according to the same cut-off ratios. All laboratory testing was performed blinded without knowledge of the vaccination status of the individual.

2.2.2. Data entry and statistical analysis

The study was co-ordinated by the Immunisation Division of the Public Health Laboratory Service Communicable Disease Surveillance Centre. Information from the clinical record cards was entered at CDSC.

Statistical analysis was undertaken in Epi-info version 6.04 [24]. Antibody levels were log-transformed for calculation of geometric mean titres (GMT), concentrations (GMC) and 95% CI. Means were compared among vaccine groups using the Students's *t*-test. Differences between vaccine groups in proportions above specified levels and other group characteristics were tested by χ^2 and Fishers exact test as appropriate.

3. Results

3.1. Pre-school booster study

3.1.1. Measles

The distribution of IgG antibody in the two groups is shown in Fig. 1a. A significantly larger proportion (8.5 and 11.1%, respectively) of those who had received only a single dose of MMR vaccine were measles IgG antibody negative or equivocal, compared with 0 and 1.4%, respectively of those who had recently received a second dose of MMR. The geometric mean antibody concentration was significantly higher in the group who had received two doses of MMR (673.7 mIU/ml, 95% CI 616.6–741.3) compared with those who had received only a single dose (289.7 mIU/ml, 95% CI 257.0–323.6) ($P < 0.00001$). Of those who had received only a single dose, the proportion who were antibody negative or equivocal was significantly higher in children vaccinated at 12 months of age than in children vaccinated at 13–17 months of age (55/186 versus 16/151, $P < 0.0001$).

Only a small proportion of either group (2.1% of one dose, 0.9% of two dose children) had IgM measles antibody. There was no significant difference between the two groups (Yates corrected $\chi^2 = 0.55$, $P = 0.46$).

3.1.2. Mumps

The distribution of IgG antibody is shown in Fig. 1b. A significantly larger proportion of single-dose children were mumps IgG antibody negative or equivocal (14.9 and 9.8%, respectively), compared with only 1.4 and 0.9%, respectively of those receiving a second dose (Table 1). Again there was a significantly higher geometric mean antibody concentration in the children who received a second dose of MMR (144.5 IU/ml) compared those who did not (37.1 IU/ml) ($P = 0.00001$). Of those who had received only a single dose, there was no significant difference in the proportion who were antibody negative or equivocal between children vaccinated at 12 months of age and children vaccinated at 13–17 months of age (40/180 versus 42/151, $P = 0.22$).

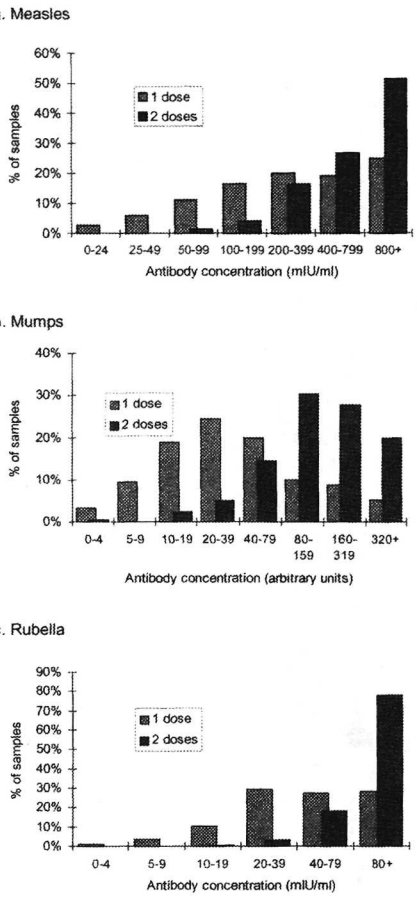

Fig. 1. (a–c) Measles, mumps and rubella IgG antibody distribution in PSB study. Comparing one dose group: 4 years post-dose 1 and two dose group: 6 weeks post-dose 2.

Table 1
The individual level antibody status of 389 children who received a single dose of MMR vaccine[a,b]

	Measles/mumps/rubella antibody status							
	+/+/+	+/+/−	+/−/+	+/−/−	−/+/+	−/+/−	−/−/+	−/−/−
Observed	230	8	73	2	52	3	16	5
Expected (independent)	224.8	10.9	73.7	3.6	54.6	2.6	17.9	0.9
Expected (final model)	230.0	8.4	71.9	2.6	52.6	1.9	16.5	5.0

[a] Positive (+), negative/equivocal (−).

[b] Number observed; number expected if seropositivity for each component was independent, and number expected allowing for a proportion of complete vaccination failures.

IgM antibody to mumps was detected only 0.4% of the children who received a MMR second dose and in none of those who did not.

3.1.3. Rubella

The distribution of IgG antibody in the two groups is shown in Fig. 1c. Only a small proportion (1.0 and 3.6%) of those receiving a single dose of MMR were rubella IgG antibody negative or equivocal compared with none of those given a second dose. However, the geometric mean antibody concentration was significantly higher in the children who received a second dose of MMR (72.4 IU/ml, 95% CI 70.8–74.1) compared to those who did not (40.7 IU/ml, 95% CI 38.0–43.6) ($P = 0.00001$). Of those who had received only a single dose, there was no significant difference in the proportion who were antibody negative or equivocal between children vaccinated at 12 months of age and children vaccinated at 13–17 months of age (7/186 versus 9/151, $P = 0.49$).

IgM antibody to rubella was detected in 4.1% of the children who received an MMR second dose and in 2.8% of those who did not. This difference was non-significant ($\chi^2 = 0.69$, $P = 0.41$).

3.1.4. Individual level analysis of MMR seropositivity

The antibody status of the 389 children who received a single dose of MMR, is shown in Fig. 1; 41% had negative or equivocal levels to one or more antigens. After a second dose of MMR vaccine, this proportion dropped to <4% (Fig. 2).

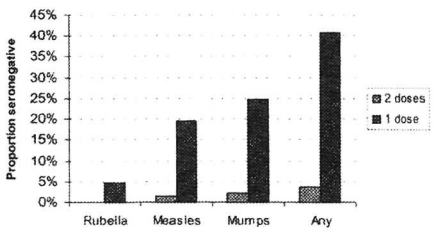

Fig. 2. Proportion antibody negative/equivocal to one or all of the three antigens by number of doses received. Comparing one dose group: 4 years post-dose 1 and two dose group: 6 weeks post-dose 2.

At the individual level, there was evidence of some dependence in the probability of seropositivity for each antigen (ΔDev = 11.4 on 4 d.f., $P = 0.02$) (Table 1). In particular, five children were negative or equivocal to all three antigens, higher than the number expected (0.9) if seropositivity to each vaccine component was entirely independent. However, after accounting for a small proportion (1%) of children who were complete vaccination failures, there was no evidence of any further dependence in the probability of seropositivity to each vaccine component (ΔDev = 0.73 on 3 d.f., $P = 0.87$) (Table 1).

3.2. National serological surveillance

For the birth-cohort born in 1989, the measles and rubella IgG antibody distributions, in 1994 before the November

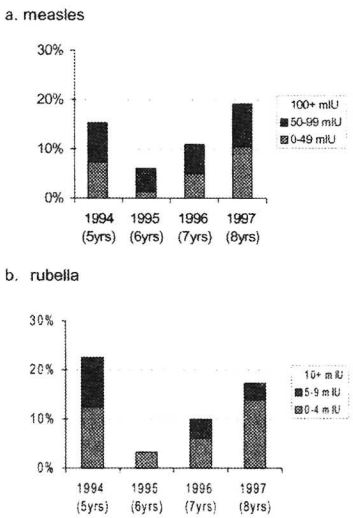

Fig. 3. (a) Proportion of age-cohort with low measles IgG antibody levels in cohort pre- and post-MR dose; (b) proportion of age-cohort with low rubella IgG antibody levels in cohort pre- and post-MR dose.

1994 MR campaign, and in the subsequent 3 years are shown in Fig. 3. A large decline in the proportion of the cohort with low or no detectable IgG antibody for measles and rubella is seen from before to after the MR campaign. There is a subsequent increase in the proportion with low or no detectable antibody over the two following years (1996–1997) back to the pre-second dose MR level. A similar observation is seen for the 1988 cohort (data not shown).

4. Discussion

This paper shows that 2–4 years after receiving a first dose of MMR vaccine, a significant proportion of pre-school children had measles and mumps IgG antibody levels below the putative level of protection, whereas few remained unprotected against rubella infection. These observations are consistent with previous immunogenicity studies in the UK [10] and Canada [25]. The higher protection afforded by a single dose of rubella vaccine is compatible with these studies where less than 1% of the study population were seronegative for rubella antibody and confirms the excellent immunogenicity of the RA 27/3 rubella strain [25].

We examined several factors that might influence seropositivity including age at vaccination and correlation with presence of antibody to the other MMR antigens. We found that pre-school children who had been immunised at 12 months of age were significantly less likely to have measles antibody than those vaccinated at 13–17 months. This is consistent with the vaccine efficacy observed in a measles outbreak in Canada [26]. However, we found no effect of age at immunisation on mumps or rubella seropositivity in pre-school children. We found no evidence for correlation of seropositivity to each antigen, other than that produced by a small excess of children negative or equivocal to all three antigens (1%). This contrasts with observations by Sauver et al. who found small but significant correlations in low antibody levels, with 0.3% of children seronegative to all three antigens [27]. The mechanism for our observations is unclear. The excess of children with low antibody levels to all three antigens may be caused by a small proportion of complete vaccination failures, due to impotent vaccine, incorrect delivery or individual factors. The independence of seropositivity in the remainder supports the suggestion that low antibody levels may be due to individual immunogenetic factors [28] or purely chance. The large proportion of children with low antibody levels for at least one antigen (41%) after receiving a single dose of vaccine supports the policy of administering a second dose of trivalent MMR vaccine to all children.

The vast majority of children who receive a single dose of MMR seem to be immunologically primed as evidenced by the lack of a significant IgM response to any of the three antigens following a second dose of MMR in the pre-school study. This significant increase in IgG levels but lack of an IgM response suggests that a large proportion of the observed population seronegativity after a single dose was due to waning antibody levels (rather than primary vaccine failure). The 4–6-week time window from administration of MMR vaccine to serum sampling should have been adequate to detect the IgM increase associated with a primary immune response, as IgM antibody levels would not have declined significantly and a large proportion would still be expected to remain seropositive [29]. Our results conflict with published evidence from some other studies: Erdman et al [11] found that amongst pre-school children who had received a single dose of vaccine, but had no detectable pre-existing antibodies, 33/36 developed IgM antibody following boosting with a dose of MMR. This suggests that the IgM assay used by Erdman was either more sensitive than ours, detecting the low levels of IgM that may be associated with secondary responses, or was less specific [30].

Administration of a second dose of MMR boosted IgG antibody to levels similar to those found 6 months after the first dose for measles and rubella and to even higher levels for mumps. This has been observed previously for each of measles [31,32], mumps [31,33] and rubella [31]. However, the increase in antibody levels does not seem to be sustained for either measles or rubella. The decline in measles and rubella antibody levels observed in our serological surveillance of children pre- and 2 years post-MMR second dose has also been documented in a longitudinal cohort study in Finland [34] and in re-vaccinated adolescents and young adults elsewhere [35,36].

How do these immunogenicity results correlate with clinical protection? Some authors have suggested that particular antibody concentrations are protective against measles disease [7]. Although it is clear from recent studies of measles outbreaks that vaccine efficacy is higher after two doses of MMR than after a single dose [37–39], within 3 years of receiving a second dose of measles containing vaccine, population antibody titres have returned to pre-second dose levels. These observations suggest that total IgG is not an entirely appropriate correlate of protection in highly vaccinated populations, since low antibody levels in vaccinated individuals are not indicative of lack of clinical protection.

With the introduction of two-dose MMR programmes in many countries with improved measles control, continued monitoring of long-term protection will be required particularly in the absence of boosting from wild virus circulating in the population. Measurement of IgG avidity, has been used to distinguish primary and secondary responses after vaccination and exposure to measles, mumps and rubella [40–42]. The role of antibody avidity testing in the evaluation of MMR vaccination strategies in a variety of populations merits further investigation.

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References

[1] Dias JA, Cordeiro M, Afzal MA, Freitas MG, Morgado MR, Silva JL, et al. Mumps epidemic in Portugal despite high vaccine coverage. Eurosurveillance 1996;1:25–8.

[2] Morse D, O'Shea M, Hamilton G, Soltanpoor N, Leece G, Miller E, et al. Outbreak of measles in a teenage school population: the need to immunise susceptible adolescents. Epidemiol Infect 1994;113(2):255–65.

[3] Matson DO, Byington C, Canfield M, Albrecht P, Feigin RD. Investigation of a measles outbreak in a fully vaccinated school population including serum studies before and after revaccination. Pediatr Infect Dis J 1993;12(4):292–9.

[4] Hersh BS, Fine PE, Kent WK, Cochi SL, Kahn LH, Zell ER, et al. Mumps outbreak in a highly vaccinated population. J Paediatr 1991;119(2):187–93.

[5] Cheek JE, Baron R, Atlas H, Wilson DL, Crider RD. Mumps outbreak in a highly vaccinated school population: evidence of large-scale vaccination failure. Arch Paediatr Adolesc Med1995;149(7): 774–8.

[6] Ward BJ, Boulianne S, Ratnam S, Guiot MC, Couillard M, De Serres G. Cellular immunity in measles vaccine failure: demonstration of measles antigen-specific lymphoproliferative responses despite limited serum antibody production after revaccination. J Infect Dis 1995;172:1591–5.

[7] Chen RT, Markowitz LE, Albrecht P, Stewart JA, Mofenson LM, Preblud SR, et al. Measles antibody: re-evaluation of protective titers. J Infect Dis 1990;162(5):1036–42.

[8] Broliden K, Abreu ER, Arneborn M, Bottiger M. Immunity to mumps before and after MMR vaccination at 12 years of age in the first generation offered the two dose immunisation programme. Vaccine 1998;16(2–3):323–7.

[9] Edees S, Pullan CR, Hull D. A randomised single blind trial of a combined mumps, measles, rubella vaccine to evaluate serological response and reactions in the UK population. Public Health 1991;105(2):91–7.

[10] Miller E, Hill A, Morgan-Capner P, Forsey T, Rush M. Antibodies to measles, mumps and rubella in UK children 4 years after vaccination with different MMR vaccines. Vaccine 1995;13(9):799–802.

[11] Erdman D, Heath JL, Watson JC, Markowitz LE, Bellini WJ. Immunoglobulin M antibody response to measles virus following primary and secondary vaccination and natural virus infection. J Med Virol 1993;41(1):44–8.

[12] Ozanne G, d'Halewyn MA. Secondary immune response in a vaccinated population during a large measles epidemic. J Clin Microbiol 1992;30(7):1778–82.

[13] Markovitz L, Preblud S, Fine P, Orenstein W. Duration of live measles vaccine-induced immunity. Paediatr Infect Dis 1990;9:101–10.

[14] Paunio M, Hedman K, Davidkin I, Valle M, Heinonen OP, Leinikki P, et al. Secondary measles vaccine failures identified by measurement of IgG avidity: high occurrence among teenagers vaccinated at a young age. Epidemiol Infect 2000;124:263–71.

[15] Edmonson MB, Addiss DG, McPherson JT, Berg JL, Circo SR, Davis JP. Mild measles and secondary vaccine failure during a sustained outbreak in a highly vaccinated population. JAMA 1990;263(18):2467–71.

[16] Mossong J, Nokes DJ, Edmunds WJ, Cox MJ, Ratnam S, Muller CP. Modelling the impact of subclinical measles transmission in vaccinated populations with waning immunity. Am J Epidemiol 1999;150(11):1238–49.

[17] Poland GA, Jacobson RM. Failure to reach the goal of measles elimination: apparent paradox of measles infections in immunised persons. Arch Intern Med 1994;154(16):1815–20.

[18] Peltola H, Heinonen OP, Valle M, Paunio M, Virtanen M, Karanko V, et al. The elimination of indigenous measles, mumps and rubella from Finland by a 12 year, two-dose vaccination programme. N Engl J Med 1994;331(21):1397–402.

[19] Ramsay M, Gay NJ, Miller E, White J, Morgan-Capner P, Brown DW. The epidemiology of measles in England and Wales: rationale for the 1994 national vaccination campaign. CDR Rev 1994;4(12):141–6.

[20] Miller E, Waight P, Laurichesse H, Andrews N, Thornton C, Sesardic D, et al. Immunogenicity and reactogenicity of acellular diphtheria/tetanus/pertussis vaccines given as a pre-school booster: effect of simultaneous administration of MMR. Vaccine 2001;19(28–29):3904–11.

[21] Osborne K, Gay NJ, Hesketh LM, Morgan-Capner P, Miller E. 10 years of serological surveillance in England and Wales: methods, results, implications and action. Int J Epidemiol 2000;29(2):362–8.

[22] Andrews N, Pebody RG, Berbers G, Blondeau C, Crovari P, Davidkin I, et al. The European Sero-Epidemiology Network: standardising the enzyme immunoassay results for measles, mumps and rubella. Epidiol Infect 2000;125:127–43.

[23] Perry KR, Brown BWG, Parry JV, Panday S, Pipkin C, Richard A. Detection of measles, mumps and rubella antibodies in saliva using antibody capture radioimmunoassay. J Med Virol 1993;40:235–40.

[24] Dean AG, Dean JA, Coulombier D, et al. Epi-Info, version 6.03: a word processing, database and statistics programme for epidemiology on microcomputers. Centres for Disease Control and Prevention, Atlanta, GA, USA, 1995.

[25] Mitchell LA, Tingle AJ, Decarie D, Lajeunesse C. Serologic reponses to measles, mumps and rubella (MMR) vaccine in healthy infants: failure to respond to measles and mumps components may influence decisions on timing of the second dose of MMR. Can J Public Health 1998;89(5):325–8.

[26] De Serres G, Boulianne N, Meyer F, Ward BJ. Measles vaccine efficacy during an outbreak in a highly vaccinated population: incremental increase in protection with age at vaccination up to 18 months. Epidemiol Infect 1995;115(2):315–23.

[27] Sauver J, Jacobson R, Vierkant R, Jacobson S, Green E, Schaid D, et al. Correlations between measles, mumps and rubella serum antibody levels in Olmsted County school children. Vaccine 2001;19:1363–8.

[28] Tan P, Jacobson RM, Poland GA, Jacobsen SJ, Pankratz VS. Twin studies of immunogenicity—determining the genetic contribution to vaccine failure. Vaccine 2001;19(17–19):2434–9.

[29] Helfand RF, Gary HE, Atkinson WL, Nordin JD, Keyserling HL, Bellini WJ. Decline of measles-specific immunoglobulin M antibodies after primary measles, mumps and rubella vaccination. Clin Diagn Lab Immunol 1998;5(2):135–8.

[30] Thomas HIJ, Morgan-Capner P, Hesketh LM. Persistent rubella-specific IgM reactivity in the absence of recent rubella and rubella reinfection. J Med Virol 1992;36:188–92.

[31] Johnson CE, Kumar ML, Whitwell JK, et al. Antibody persistence after primary measles–mumps–rubella vaccine and response to a second dose given at 4–6 months versus 11–13 years. Paediatr Infect Dis J 1996;15(8):687–92.

[32] De Serres G, Sciberras J, Naus M, Boulianne N, Duval B, Rochette L. Protection after two doses of measles vaccine is independent of interval between doses. J Infect Dis 1999;180:187–90.

[33] Davidkin I, Valle M, Julkunen I. Persistence of anti-mumps virus antibodies after a two-dose MMR vaccination: a 9-year follow-up. Vaccine 1995;13(16):1617–22.

[34] Davidkin I, Valle M. Vaccine-induced measles virus antibodies after two doses of combined measles, mumps and rubella vaccine: a 12-year follow-up in two cohorts. Vaccine 1998;16(20):2052–7.

[35] Cohn ML, Robinson ED, Faerber M, et al. Measles vaccine failures: lack of sustained measles-specific immunoglobulin G responses in revaccinated adolescents and young adults. Paediatr Infect Dis J 1994;13(1):34–8.

[36] Christenson B, Bottiger M. Measles antibody: comparison of long-term vaccination titres, early vaccination titres and naturally acquired immunity to and booster effects on the measles virus. Vaccine 1994;12(2):129–33.

[37] Vitek CR, Aduddell M, Brinton MJ, Hoffman RE, Redd SC. Increased protections during a measles outbreak of children previously vaccinated with a second dose of measles–mumps–rubella vaccine. Pediatr Infect Dis J 1999;18(7):620–3.

[38] Paunio M, Peltola H, Valle M, Davidkin I, Virtanen M, Heinonen OP. Twice vaccinated recipients are better protected against epidemic measles than are single dose recipients of measles containing vaccine. J Epidemiol Community Health 1999;53(3):173–8.

[39] Hennessey KA, Ion-Nedelcu N, Craciun M, Toma F, Wattigney W, Strebel P. Measles epidemic in Romania, 1996–1998: assessment of vaccine effectiveness by case-control and cohort studies. Am J Epidemiol 1999;150:1250–7.

[40] Matter L, Kogelschatz K, Germann D. Serum levels of rubella virus antibodies indicating immunity: response to vaccination of subjects or undetectable antibody concentrations. J Infect Dis 1997;175:749–55.

[41] de Souza V, Pannuti C, Sumita L, de Andrade H. Enzyme-linked immunosorbent assay-IgG antibody avidity test for single sample serologic evaluation of measles vaccines. J Med Virol 1997;52:275–9.

[42] Narita M, Matsuzono Y, Takekoshi Y, Yamada S, Itakura O, Kubota M, et al. Analysis of mumps vaccine failures by means of avidity testing for mumps virus-specific immunoglobulin G. Clin Diagn Lab Immunol 1998;5:799–803.