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ORIGINAL ARTICLE

Identifying risk factors associated with acquiring measles in an outbreak among age-appropriately vaccinated school children: a cohort analysis

Bernadette O'Connor[1] · Sarah Doyle[1]

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Abstract

Background A measles outbreak occurred in age-appropriately vaccinated children in a school in a town in the South East of Ireland in September–November 2013.

Aims The purpose of this study was to investigate the risk factors associated with catching measles during the outbreak.

Methods Ninety-five children (4–5 years) in three classes, in the first year of primary school, were included in the study. Immunisation records on the South East Child Health Information System for first Measles Mumps and Rubella (MMR) vaccine for the 95 children were reviewed. Data collected included age at MMR, date of administration of MMR, MMR brand and batch number, and the General Practice at which MMR was administered. The risk factors analysed included age at vaccination, time of vaccination, class and the GP practice where MMR was administered. Statistical analysis was performed using Epi info 7 and SPSS v24.

Results Thirteen children in the cohort developed measles during the outbreak. All children in the cohort were age-appropriately vaccinated, with one dose of MMR vaccine. Analysis demonstrated statistically significant differences in the relative risk of developing measles according to the class a child was in, and the General Practice at which they were vaccinated.

Conclusions The reason for intense measles activity in one class was not established. Although a concurrent investigation into cold chain and vaccine stock management did not identify a cause for the high relative risk of measles in children vaccinated, recommendations were made for improving cold chain and vaccine stock management in General Practices.

Keywords Cohort · Measles · Outbreak · Vaccination

Introduction

A measles outbreak occurred in age-appropriately vaccinated children in a school in a small town in the South East of Ireland in September–November 2013 [1]. Measles Mumps Rubella (MMR) vaccine uptake at 24 months was between 85 and 94%, annually from 2009 to 2012, in the region where the outbreak occurred [2]. When measles outbreaks occur in areas with high vaccination coverage, the outbreaks rarely spread beyond those who are unvaccinated [3].

MMR vaccine was introduced in Ireland in 1998. It is given to babies at 12 months of age, with a second dose given in the first year of primary school (Junior Infants), at 4–5 years of age. One dose of MMR will provide immunity to approximately 95% of individuals, with two doses giving protection in about 99% of people [4].

It has been reported that there is a greater risk of vaccine failure; the younger one is at age of vaccination [5]. Proper storage and handling practices for all vaccines are important, to maintain vaccine potency and effectiveness. MMR vaccine must be kept refrigerated at + 2 to + 8 °C, protected from light and used within 1 h of reconstitution [6].

This paper presents the results of a cohort study undertaken during the outbreak. The detail of the outbreak is presented elsewhere [1]. In summary, there were 20 cases of measles in the outbreak, 15 of whom attended the index school, School Q. This is one of three primary schools in the town [1]. Fourteen of the 15 cases occurred in the three classes, classes E, F and G, in the Junior Infant year.

In Ireland, Junior Infants is the first year of primary school, which children start at age 4–5 years. The school vaccination team was scheduled to attend the school for administration of

✉ Sarah Doyle
sarahm.doyle@hse.ie

[1] Department of Public Health, Health Service Executive South East, Lacken, Dublin Road, Kilkenny R95 P231, Ireland

the second dose of MMR to children in the Junior Infant classes later in the academic year.

During the outbreak, a cohort of vaccinated children in Junior Infants (which constituted a majority sub-group of cases in the outbreak) was identified. It was decided to study this cohort to identify factors potentially associated with developing measles in age-appropriately vaccinated children in the outbreak. The results of this study are presented here.

Methods

Study population

There was a total of 98 students in three Junior Infant classes in School Q. One student (a case) was unvaccinated with MMR and two (not cases) had received MMR outside the South East area (therefore, not exposed to the same vaccination factors as the other children in the school) and so were excluded from the study. This resulted in a total of 95 students, 13 of whom were measles cases (11 confirmed, 2 probable) in the cohort study. All 95 students had received their first MMR as part of the primary vaccination programme.

Sixty-eight students in the cohort population received their first MMR vaccine from General Practitioners (GPs) at four General Practices in the town (practices W, X, Y and Z). Twenty-seven students received MMR from practices based in a neighbouring city. Only two of the latter GPs vaccinated more than three children in the cohort each.

The case definition and classification for the cohort study were as for the outbreak: a person with fever > 38 °C and rash and one of the following: conjunctivitis, cough, coryza with onset since 1 September 2013, residing in the town [1]. The case classification is as defined in Case Definitions for Notifiable Diseases, HPSC, 2012 [7].

Data collection

Immunisation records on the South East Child Health Information System for first MMR for the 95 children in the cohort were reviewed. Data collected included age at MMR, date of administration of MMR, MMR brand and batch number, and the General Practice at which MMR was administered.

Data analysis

Univariate, bivariate, stratified and multivariate analyses were performed using Epi info 7 and SPSS v24. Stepwise forward logistic regression (SPSS v24) was used to study the potentially confounding effects of the variables measured in this study on each other. The model used was developed based on the results of the univariate, bivariate and stratified analyses. Interactions between variables were also examined but did not contribute to the final model.

Attack rate and vaccine effectiveness

The attack rate and vaccine effectiveness were calculated for the three Junior Infant classes and for the Junior Infant year in School Q. It was not possible to directly calculate vaccine effectiveness for this cohort population as there were no unvaccinated children in the group. Therefore, vaccine effectiveness was calculated assuming an attack rate of 90% in the unvaccinated population [1, 8].

Results

Figure 1 displays the epidemiological curve for the cohort population. All children received a second MMR, administered by the school immunisation team as part of the outbreak control measures, on 18 October 2013 [1].

There were 13 cases of measles in the Junior Infant cohort during the outbreak, 11 in class E, one in class F and one in class G (Table 1). Cases and non-cases in the cohort were of similar age and gender. The clinical presentation of cases was with relatively mild illness, with only one with a complication (otitis media) [1].

The attack rate for the cohort was 14%, with attack rates for classes E, F and G 36, 3 and 3%, respectively. One dose MMR vaccine effectiveness against measles was 84% in this group. Vaccine effectiveness was 60% in class E and 97% in classes F and G. Vaccine effectiveness for practices X and Y was 51 and 74%, respectively, compared to 97% for all other GPs (Table 2).

Risk factors evaluated

The variables evaluated as potential risk factors in acquiring measles in the cohort selected included age at vaccination, Junior Infant class, the General Practice where MMR was administered, MMR batch and time of MMR vaccination.

Age at vaccination

Defay et al. (2013) have previously observed that there is a greater risk of vaccine failure; the younger one is at age of vaccination [5]. Therefore, the median age at time of first MMR was compared for cases and non-cases for the cohort, for those vaccinated by practices X and Y and for class E. The median age (months) at vaccination was higher in cases in the cohort, and in those vaccinated by GP practices X and Y, but the differences were not statistically significant (Table 1).

Analysis of the risk of developing measles at a younger age at vaccination was also performed by categorising children into

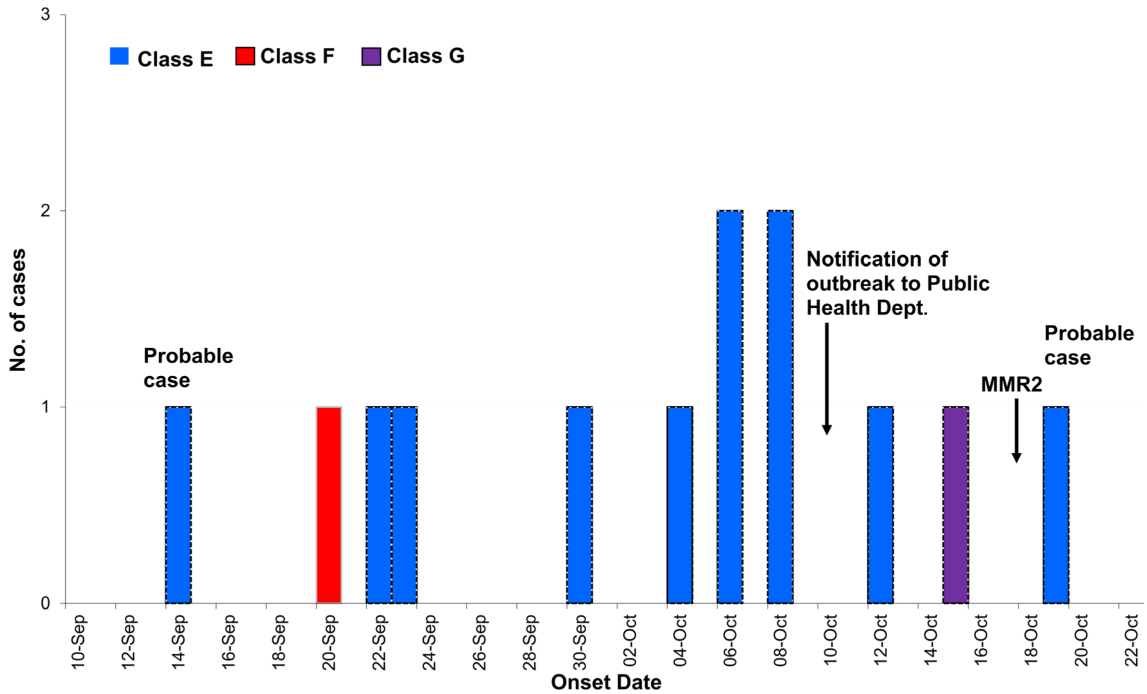

Fig. 1 Case onset dates and classes of measles cases in cohort study ($n = 13$), measles outbreak, South East Ireland, September to November 2013

groups according to age at vaccination and determining relative risk of developing measles according to those categories. Although the relative risk of developing measles for those vaccinated under 15 months compared to those vaccinated at 15 months or over was high (2.25), the difference was not statistically significant, with wide confidence intervals (95% CI 0.32–16.04). In a sensitivity analysis, a similar result was obtained when those aged 14 months at vaccination were excluded.

Table 1 Demographic details of cohort population ($n = 95$), measles outbreak, South East Ireland, September to November 2013

	Case	Non-case
Total	13	82
Confirmed	11	–
Probable	2	–
Male	7	42
Female	6	40
Mean age (months)	59.7	59.6
Class E	11	20
Class F	1	32
Class G	1	30
Date 1st MMR	07/08/09–11/02/10	12/02/09–01/06/11
Median age* 1st MMR cohort	13.7	12.6
Median age* 1st MMR practice X	13.7	13.1
Median age* 1st MMR practice Y	13.9	12.5
Median age* 1st MMR class E	13.6	13.6

*Median age in months

Class

There was a highly statistically significant association identified between being in class E and developing measles in this cohort, compared to classes F and G (RR = 11.35, 95% CI 2.68–48.13, $p < 0.001$). Stratification of the class analysis by age at MMR did not impact on these results.

The earliest onset of measles symptoms was in a pupil in class E on 14 September 2013 with the last onset date being 19 October 2013. The onset dates for each of the cases in class F and class G were 20th of September and 15th of October, respectively. It is known that a second, unvaccinated case in class G was not at school during any of the infectious period of illness. Pupils in each of classes F and G were exposed to only one infectious case of measles, contrasted with 11 in class E over a period of a month, during the outbreak. It is not known for how many days children were in school while infectious, but it is known that there was considerably more prolonged exposure for the children in class E.

General practice where children were administered MMR

The highest percentages of measles cases occurred in children vaccinated by practices X and Y, with 44 and 23%, respectively, of those vaccinated by these practices developing measles.

The relative risk of developing measles if vaccinated by practice X, compared with all other practices (excluding Y), was 14.22 (95% CI 3.31–61.16) (Table 3). The relative risk of

Table 2 MMR vaccine effectiveness

	All classes (%)	Class E (%)	Class F (%)	Class G (%)
All GPs	84	60	97	97
Practice X	51	4	84	72
Practice Y	74	33	100	100
GPs (excl. practices X and Y)	97	88	100	100

developing measles if vaccinated by practice Y, compared with all other practices (excluding X) was 7.38 (95% CI 1.37–39.90). Stratification of GP practice analysis by age at first MMR did not impact on these results. However, the relative risk of being a case if vaccinated by practice X for those in class E was 4.1 (95% CI 1.8–9.5). The percentage of children vaccinated by practice X or practice Y was higher in class E (39%) compared to classes F (30%) and G (29%).

MMR batch

There were two different brands of MMR vaccine used to vaccinate the children in this cohort, GlaxoSmithKline Priorix and Sanofi MSD MMRvaxPro. Fifteen batch numbers of Priorix, and five batch numbers of MMRvaxPro, were used. All cases of measles had been vaccinated with one of three batch numbers of Priorix, or of two batch numbers of MMRvaxPro. There were three batch numbers of MMR where there was more than one case of measles. All relative risks of developing measles if vaccinated by one of these batch numbers were raised, but none was statistically significant. Vaccines from the same batch are distributed to GPs, and so multivariate analysis (see below) is important for interpretation of this result.

Time interval of MMR vaccination

MMR vaccination was administered between 07/08/2009 and 11/02/2010 for cases and between 12/02/2009 and 01/06/2011 for non-cases; a considerably narrower time interval for cases. We speculated that there may have been an unidentified problem that occurred at this time, for example with the cold chain, or with management of vaccines within GP practices (e.g. by temporary staff members). An analysis was performed to estimate the relative risk of developing measles if vaccinated between 01/07/09 and 31/12/09 or between 01/01/10 and 30/06/10 (against all other dates). There was no difference between the relative risk of contracting measles if vaccinated within these time intervals and that of contracting it if vaccinated on other dates. However, when these time intervals were stratified by class, children in class E, vaccinated between 01/07/09 and 31/12/09, were more likely to develop measles (RR = 2.77, 95% CI 1.3–7.5, $p < 0.05$).

Multivariable analysis

Stepwise forward logistic regression (SPSS v24) was used to study the potentially confounding effects of the variables measured in this study on each other. The model used was developed based on the results of the univariate, bivariate and stratified analyses. Interactions between variables were also examined but did not contribute to the final model.

In the multivariable analysis, the final model included only GP practice and class, as other variables did not have an important effect on it. There was a statistically significantly raised adjusted odds ratio of contracting measles if vaccinated in practice X or in practice Y and if in class E (Table 4). The confidence intervals for all results are wide.

In a sensitivity analysis, all calculations were repeated to include just confirmed (and not probable) cases. The findings were similar.

Discussion

The children in Junior Infants formed a discrete cohort and were, therefore, selected to investigate possible causative factors associated with development of measles in vaccinated children in this outbreak. Documented immunisation records on this cohort population provided the opportunity to conduct an analysis of the potential association between measles infection, age at vaccination, Junior Infant class, MMR batch and time of MMR vaccination, and the General Practice where MMR was administered.

The overall attack rate, in a vaccinated population, of 14% for the cohort and 36% for class E are much higher than that

Table 3 Risk of developing measles by practice who administered MMR

MMR by practice	*n*	Relative risk (95% CI)	*p* value
Practices (excl. practices X and Y)	64	1	–
Practice X	18	14.22 (3.31–61.16)	$p < 0.001$
Practice Y	13	7.38 (1.37–39.90)	$p < 0.05$

Table 4 Multivariable analysis of risk of developing measles by GP practice and class

	n	Odds Ratio (95% CI)	Significance
Practice X	18	83.88 (6.83–1030.80)	$p < 0.01$
Practice Y	13	11.33 (1.26–101.95)	$p < 0.05$
Class E	31	38.47 (2.55–580.33)	$p < 0.01$

expected due to vaccine failure [1, 8]. The low vaccine effectiveness (VE) in class E (60%) resulted in children in this class being more susceptible to measles. Studies have shown that potential reasons for low VE include vaccine failure, waning of immunity or cold chain inadequacies [9, 10].

The clinical illness in all cases in the cohort was mild, with a complication (otitis media) occurring in only one case [1]. While the lack of severity of disease in cases in this outbreak may indicate some protection from MMR, consideration also needs to be given to vaccine failure. Approximately 2–5% of children who receive one dose of MMR fail to develop an appropriate immune response [8]. This is primary vaccine failure (PVF) [8]. Secondary vaccine failure (SVF) is the waning of vaccine-induced immunity to non-protective levels [11] and occurs in vaccinated individuals [12]. Although studies have shown that, after one dose of MMR, vaccine immunity may wane over time in children; it is rare and does not tend to be a major factor in measles transmission and outbreaks [3, 12]. Measles cases resulting from SVF tend to be mild and cases are often missed, with limited transmission [12]. Distinguishing between PVF and SVF is complex and requires laboratory investigation [11]. This consists of antibody avidity measurements, where low avidity IgG antibody detection suggests PVF and high avidity antibody suggests SVF [11]. Primary MMR vaccine failure can occur due to a number of reasons, including passive antibody in the vaccine recipient, loss of efficacy and potency of the vaccine due to mishandling or storage, and inaccurate immunisation records [8]. It is possible that the cases in this cohort were due to PVF as SVF would not be expected at such a young age.

The importance of the age at administration of first dose of measles vaccine has previously been reported [5, 10], with a significant association between measles risk and the age at which the first dose was administered [10]. De Serres et al. reported that there is a significantly higher risk of developing measles in those who received the first dose of vaccine at 12 months of age compared to those who were vaccinated at 15 months of age [10]. We investigated whether there was a difference in age at first vaccination in different classes, or in those vaccinated in different GP practices but this did not explain the differences in risk of measles with each of these variables.

Children in class E were more likely to contract measles during the outbreak, than those in classes F and G. The reason for this was explored, but not established; the teacher was not infected and there was no apparent difference in the classrooms or in the cohorts of children in the classes. Class registers were examined with the school principal to ensure that no cases of measles had been missed by the outbreak control team. The index case (class E) infected four others, two of whom were in class E, and one in class F. Each of the two cases infected in class E infected, on average, three others each in that class. However, the case in class F, who had onset early in the outbreak (before any outbreak control measures were instituted, as opposed to the case in class G), appears not to have infected anyone in their class. The network structure (clustering in the different classrooms, mixing of children, association with cases outside school, and household contact with siblings also attending School Q), in the three classes may have influenced the high transmission of measles in class E compared to the other two classes [13, 14]. This intense transmission in class E was unusual, as studies have suggested that it is difficult for a measles outbreak to spread in the community if vaccination rates are high in school children [15]. However, Ong et al. illustrated that it is possible for a small outbreak to occur in a setting where susceptible individuals are grouped, despite high MMR primary dose vaccination in the population [16]. While details on the exact amount of time spent by infectious cases in each classroom were not determined, it can be seen that the potential for exposure to infectious cases was much greater in class E than in either of the other two classes. As previously suggested by the authors [1], it is possible that there were more cases of measles in class E due to prolonged and intense exposure among children in class E to the measles virus prior to notification of the outbreak.

Children in this cohort who were immunised in two GP practices (X and Y) had a high odds ratio of contracting measles when compared with all other GP practices that immunised children in the cohort. Forty-four percent (8/18) of individuals in the Junior Infant cohort vaccinated by practice X and 23% (3/13) of those vaccinated by practice Y contracted measles. Of those vaccinated by practices X and Y in class E, 86% (6/7) and 60% (3/5), respectively, contracted measles. The high attack rate in class E suggests low protection for MMR after one dose, as approximately 95% of individuals are expected to develop immunity to measles after one dose of MMR [3]. However, in classes F and G 14 and 25% respectively of those vaccinated by practice X and none of the eight children vaccinated by practice Y contracted measles. Measles was introduced late into class G, i.e. a sibling of a case in class E developed measles but was infectious in class only after a second MMR had been administered to his classmates. However, this was not the case in class F where seven children were vaccinated by practice X and three by practice Y. Therefore, in class F, it appears that one dose of MMR provided reasonable protection against measles.

The risk of developing measles if vaccinated by a specific brand/batch number of MMR was also analysed, with no statistically significant result found. Furthermore, GlaxoSmithKline and Sanofi MSD investigated the batches of Priorix and MMRvaxPRO associated with the 13 measles cases and confirmed that there were no quality issues with these batches of vaccines that could have contributed to lack of efficacy or potency in the vaccines.

There is a statistically significantly raised adjusted odds ratio of contracting measles if vaccinated in practice X 83.88 (95% CI 6.83–1030.80, $p < 0.01$) or in practice Y 11.33 (95% CI 1.26–101.95, $p < 0.05$), and if in class E 38.47 (95% CI 2.55–580.33, $p < 0.01$) (Table 4). The time interval during which non-cases got MMR was much wider than for cases. For the cohort, there was no significant difference between the relative risk of contracting measles if vaccinated within a 6-month time interval during which cases received MMR compared to other 6-month time intervals during which MMR was given. However, children in class E vaccinated between 01/07/09 and 31/12/09 were more likely to develop measles (RR = 2.77, 95% CI 1.3–7.5, $p < 0.05$). In line with the National Immunisation Guidelines of Ireland, 92% of the cohort received other vaccines on the same day that they received MMR [4]. The vaccines simultaneously administered were Pneumococcal Conjugate vaccine (PCV), Haemophilus Influenzae B Booster (HIBB) and Meningococcal C (MenC). There were no notifications of any of these other infections in any of these children; although given the small numbers and infrequency of notification of these infections, it is hard to be conclusive that this implies adequate protection against them. There was a vaccine storage-related episode reported by practice X that occurred during the time interval when children were vaccinated. However, following the episode, all unused vaccine was returned to the National Immunisation Office. No vaccines from the returned batch were administered by practice X to any of the measles cases or to any of the non-cases in the cohort.

Errors in the management and administration of MMR vaccine in general practice can potentially affect the effectiveness of the vaccine [17]. An investigation of MMR vaccine management and administration, of all batches of MMR given to the cases in the cohort population, was conducted by the National Immunisation Office. Although some deficiencies in stock management were identified, the investigation did not identify any vaccine management and administration practices that explained the higher risk of measles infection in children vaccinated in practices X and Y. However, it was not possible to investigate in-practice vaccine management.

There are some limitations to the study. Electronic immunisation records on the Child Health Information System were reviewed for all children in the cohort. While this data is accurate, it is limited compared to information and data that might be collected, if questionnaires were conducted with the children's parents/guardians. Also, maternal antibodies interfere with measles vaccine and are typically lower in children born to vaccinated as compared to previously infected mothers, but maternal data was not collected [10, 13, 15, 18, 19]. As there were no unvaccinated children in this cohort and vaccine effectiveness was calculated assuming an attack rate of 90% in the unvaccinated population [8], it is possible that vaccine effectiveness was underestimated [10, 20]. The discussion on PVF and SVF cannot be substantiated in the absence of antibody avidity IgG measurements [17].

Conclusions

The reason for intense measles activity in class E in the index school, as opposed to class F in particular, was not established. The reason for a high odds ratio of measles in patients immunised by practices X and Y was not identified. Nothing in the investigation indicated why this was so. While some deficiencies in stock management were identified, these were not unique to these general practices. There may be other confounding factors, not measured during this outbreak, that account for the increases. The possibility of problems at practice X within the time interval identified may account for a decrease in vaccine effectiveness.

Children in this cohort vaccinated by practice X have all now received a second MMR. There continues to be a high uptake of MMR in the area and practice X is no longer in operation.

Development of an audit tool and training for GPs and practice nurses in cold chain and vaccine stock management, with inclusion of these in the general practice immunisation contract, are recommended.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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