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Risk factors for transmission of measles during an outbreak: matched case–control study

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SUMMARY

Background: In 2012, an outbreak of measles occurred in Merseyside, UK with 359 confirmed cases by 30 June. Numerous cases reported visits to healthcare and social settings.

Aim: To identify risk factors associated with measles transmission during the outbreak.

Methods: In April 2012, a retrospective matched case–control study was conducted. Fifty-five confirmed cases and 55 community controls, matched 1:1 for age and geography, were selected at random. Data on exposures in the two weeks before illness, including attendance at a healthcare setting, were collected via telephone interview. Univariate and multi-variate analyses were conducted and odds ratios were calculated.

Findings: Forty-two cases and 42 matched controls were contacted successfully. Univariate exact conditional logistic regression analysis identified that cases were more likely to have attended an emergency department, been admitted to hospital and be incompletely vaccinated (for age). Multi-variate analysis found three factors to be independently associated with measles infection: incomplete/partial vaccination for age [adjusted odds ratio (aOR) 22.1, 95% confidence interval (CI) 3.8–∞, $P < 0.001$], under age for routine vaccination (aOR 20.4, 95% CI 2.0–∞, $P = 0.009$) and hospital admission (aOR 20.2, 95% CI 1.4–∞, $P = 0.025$).

Conclusions: Incomplete/partial vaccination, under age for routine vaccination and hospital admission were associated with measles infection. These findings highlight the importance of timely vaccination of eligible individuals, early diagnosis, timely isolation of cases, and implementation of strict infection control measures.

Introduction

Measles is a highly infectious systemic viral disease spread by airborne transmission. However, routine vaccination in many developed countries has meant that measles has become relatively uncommon. In England, prior to the introduction of measles vaccination (i.e. in the 1960s), there were an estimated 300,000 measles notifications per year and scores of associated deaths.[1] Following the introduction of the single-dose measles vaccine in 1968, the number of cases of measles decreased significantly, and the introduction of the combined measles mumps and rubella (MMR) vaccine in 1988 continued this trend.[1] Unfortunately, following a high-profile paper in 1998 linking the MMR vaccine to autism and the development of bowel disorders, vaccination coverage in England declined, reaching as low as 80% in 2003/2004.[2,3] The

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claims in the paper were later discredited and the paper was retracted by the publishers.[4,5]

At the start of the 21st Century, the number of confirmed measles cases in England was as low as approximately 100 per year. This number has since increased, reaching a peak of 1330 cases in 2008; in 2011, there were 1067 cases (1.7 per 100,000 population).[6] During the last 10 years, there have been a number of small outbreaks across the country, particularly in travelling communities. In recent years, vaccine coverage has increased again (92% in 2011), but this has coincided with an increase in the number of cases of measles.[7]

This case–control study was initiated as part of the wider public health investigation into the largest measles outbreak in Merseyside (North West England) since the introduction of the MMR vaccine in 1988. The first few cases were seen in January 2012, and by the end of June, there had been 359 confirmed cases of measles in the area.[8] This compares with an average of nine confirmed cases per year over the previous five years.[9] As of the end of June 2012, over one-third of cases were children aged under five years and 30% of cases were aged 15 years or older.[8] Cases were predominantly resident in Liverpool and Sefton, and were mainly sporadic with a few outbreaks in nurseries and family clusters. Interestingly, the strain identified in many of the cases was B3, the predominant strain found on the African continent.[10] The B3 strain has been identified in cases from outbreaks in other European countries such as Spain in 2011, but it is distinct from strains identified in other parts of England during the same time frame as the outbreak in Merseyside.[8]

In order to determine the relevant risk factors associated with measles infection/transmission (including community settings), a case–control study was undertaken at an early stage of this outbreak. This paper reports the findings of the case–control study.

Methods

Case definition and identification

A case was defined as a person living in Merseyside with microbiological confirmation of measles (oral fluid/blood test immunoglobulin M positive or polymerase chain reaction positive) between 1 January and 14 March 2012 with no history of vaccination within six weeks of diagnosis. Cases were identified with a computerized case management database, used by Cheshire & Merseyside Health Protection Team (CMHPT). As the assessment focused on possible transmission settings, cases were excluded from the study if they had travelled outside of the UK in the two months preceding the onset of illness. In total, there were 71 confirmed cases of measles in Merseyside; one case was excluded from the study due to travel outside of the UK, leaving 70 cases for random allocation in the study.

Selection of controls

Controls were defined as asymptomatic persons (no history of fever and rash) with no history of travel outside of the UK in the two months preceding the onset of illness in the matched case. The controls were selected at random, matched by general medical practice and age (within one year). To ensure that all cases were matched to an appropriate number of controls (see below), five potential controls were identified for each case to allow for those who refused to participate or were untraceable; if information could not be obtained for the selected control, another control was chosen according to the same principles.

Data collection

All cases and controls were sent a letter from the CMHPT and the National Health Service (NHS) on behalf of their general medical practitioner, informing them of the purpose of the study and that they would be contacted by the local public health team if they agreed to take part. Telephone interviews were undertaken following acquisition of valid consent using an agreed script and a structured questionnaire. Information was collected on demographics and vaccination history. Data were also obtained on community and healthcare settings attended in the two weeks preceding the onset of illness in the matched case. Therefore, any case participants that were hospital inpatients prior to onset were not admitted to hospital due to the measles virus. Information was collected on demographics, vaccination history, community settings visited and attendance at healthcare settings. The interviews were conducted with a parent or guardian if the case/control was under 16 years of age. Data were entered real-time into a confidential secure web-based survey tool and database.[11]

Sample size

A sample size calculation was conducted to assess the number of cases and controls needed to achieve a minimum detectable odds ratio of 4 (at 5% significance level) for a matched study with a case–control ratio of 1:1. Assuming a 50% exposure level among controls, a sample size of 39 cases and 39 controls was required to achieve 80% power. As such, 55 cases were selected at random to allow for cases/controls that might be untraceable or refuse to participate.

Statistical analysis

To identify potential risk factors for measles infection, exact conditional logistic regression was used to calculate matched crude odds ratios (mOR), 95% confidence intervals (CIs) and *P*-values using the likelihood ratio test. Exact conditional logistic regression was identified as the most appropriate technique for a small number of cases and controls. Variables that were significant at a level of $P < 0.2$ on univariate analysis and/or known to be associated with increased risk of measles infection in the literature were selected for multi-variate regression. The final model was selected by a forward stepwise procedure, and no interaction terms were considered in the analysis because of the sample size and missing data for some variables. Two-sided *P*-values of <0.05 were considered to indicate significance, and 95% CIs were calculated. All statistical analyses were performed using R Version 2.15.0 or STATA Version 12.[12,13]

Ethics

As this study examined an outbreak that had a direct impact on public health, no ethical approval was required. Cases and

controls were contacted by trained health professionals who were specifically aware of the organization's patient confidentially principles and data protection requirements. Valid consent was sought from all participants.

Results

Forty-two (78% at the time of study) cases and 42 matched controls were interviewed over a two-week period. It was not possible to contact 13 cases who had been allocated to the study ($N = 55$). No cases or controls refused to take part in the study. The demographic characteristics of cases and controls are shown in Table I. No significant differences in demographic characteristics were seen between cases and controls.

Univariate analysis

All potential exposures and risk factors for measles infection identified through the interviews were investigated in univariate analysis (Figure 1). Age >13 months and incomplete/partial vaccination for age were significantly associated (mOR 6.3, 95% CI 1.9–33.4, $P < 0.001$) with measles infection. Contact with a measles case (mOR 32.68, 95% CI 5.8–∞, $P < 0.001$) and maternal history of measles (mOR 3.0, 95% CI 1.03–10.6, $P = 0.04$) were significantly associated with measles infection. In terms of the settings attended, attendance at an emergency department (mOR 6.0, 95% CI 1.3–55.2, $P = 0.01$) and hospital admission (mOR 8.2, 95% CI 1.2–∞, $P = 0.03$) were significantly associated with measles infection. However, being under age for vaccination (<14 months) was not significantly associated with measles infection, although the mOR was elevated.

Multi-variate analysis

Nine exposures/risk factors were identified for inclusion ($P < 0.20$) in the multi-variate analysis. Forward stepwise exact conditional logistic regression beginning with history of contact with measles as the single predictor variable did not identify other variables with a significant effect when added to the model. It was then excluded from further models as it was providing a duplicate measure of setting contact and would mask any specific setting association. The final multi-variate model identified incomplete/partial vaccination for age [adjusted odds ratio (aOR) 22.1, 95% CI 3.8–∞, <0.001], under age for routine vaccination (aOR 20.4, 95% CI 2.0–∞, $P = 0.009$) and hospital admission (aOR 20.2, 95% CI 1.4–∞, $P = 0.025$) as significant risk factors for measles infection. aORs are also shown in Figure 1.

Discussion

This matched case–control study provides further strong evidence that eligible children and young adults who are unimmunized/partially immunized and those who are too young to be vaccinated are at significantly increased risk of measles infection when measles virus is circulating. As supported by the descriptive epidemiology of this outbreak, healthcare settings are likely to have played an important role in exposure to measles, transmission and spread, particularly in hospital inpatients.[8]

Although there were a small number of measles outbreaks in nurseries and playgroups in Merseyside, these settings were not found to be associated with increased risk of measles infection/transmission.

Protection against measles in those who are too young for vaccination is dependent on passive immunity from maternal antibodies and/or herd protection. This study found that being too young for vaccination increased the risk of measles infection. The large number of cases in children who were too young for routine vaccination could be explained by early waning of maternal antibodies and lower MMR vaccination coverage in children and young adults.[8,14] Waning of maternal antibodies, although more rapid in babies born to vaccinated mothers than babies born to naturally immune mothers, is an issue for both

Table I
Demographic characteristics of measles cases and matched controls, Merseyside, UK, April 2012. Figures are *N* (%) ($N = 84$)

Characteristic	Number complete	Cases ($N = 42$)	Controls ($N = 42$)
Age (months)	84		
Median		16	15.5
Lower quartile		10	10
Upper quartile		76	77.5
Sex (male)	84	22 (52)	15 (36)
Vaccination status	83		
Vaccinated appropriately for age		5 (12)	23 (56)
Incompletely/partially vaccinated for age (>13 months)		22 (52)	6 (15)
Under age for vaccination (<14 months)		15 (36)	12 (29)
Had contact with a measles case	81	26 (65)	2 (5)
No. of children aged under five years in household	84		
Median		1	1
Lower quartile		0	0
Upper quartile		1	1
Maternal age	79		
Median		30.8	30.8
Lower quartile		25.2	26.2
Upper quartile		34.7	38

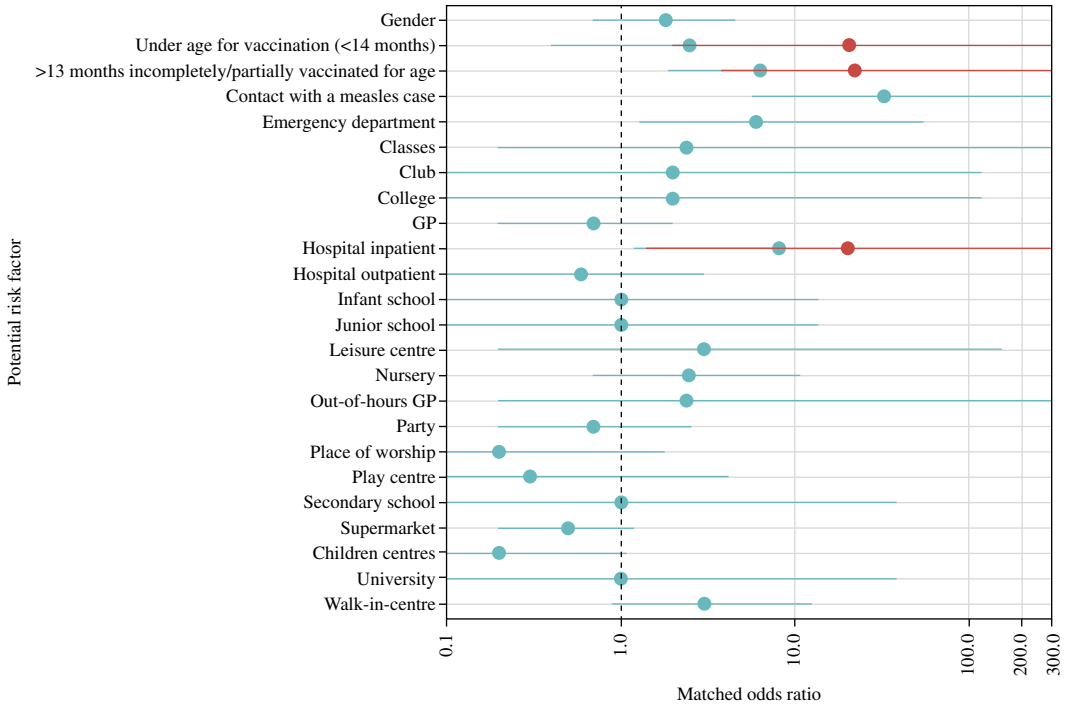

Figure 1. Univariate and multi-variate analysis of exposures/risk factors for measles infection. Adjusted OR (red line), adjusted odds ratio; crude mOR (blue line), crude matched odds ratio; GP, general practitioner.

groups. A recent study showed that over 95% of infants in both aforementioned groups had lost immunity by six months of age.[14]

Unsurprisingly, in other outbreaks of measles reported in the literature, the majority of cases were incompletely/partially vaccinated for age.[15,16] The results from this case–control study support this evidence, and show that although vaccination coverage in the case–control study area was relatively high, with 91% coverage for one dose at 24 months and 86% coverage for two doses at five years, it needs to be improved and sustained.[7] It should be noted that since the outbreak started, vaccination coverage in the study area has increased to 96% for one dose at 24 months and 91% for two doses at five years.[7] This increase is likely to have been influenced by greater vaccination efforts and media coverage of the outbreak.[8] This, however, is still below the goal of 95% coverage for two doses set by the World Health Organization European Region to eradicate measles transmission by 2015.[17] It is important to recognize that vaccination uptake does not consider cohorts of children who may have missed vaccination in previous years; these cohorts continue to accumulate and form a large subsection of the population in areas as densely populated as Merseyside. This study and descriptive epidemiology of the outbreak show that a number of cases were in this category.[8]

Most other studies looking at measles exposure in healthcare settings have implicated emergency departments as a risk for outbreak spread.[18–22] This study identified an independent significant association between measles infection and hospital admission. The opportunity for the transmission of airborne diseases such as measles is high in healthcare settings, and this risk is increased as a highly infectious disease such as measles is difficult to differentiate clinically from other viral infections.[8,20] Outbreaks reported in the literature, particularly in the USA, have highlighted that clinicians have limited experience with measles due to high vaccination coverage and rarity of outbreaks, contributing to delays in diagnosis and appropriate isolation procedures.[21,22] Measles cases are also uncommon in the UK, and it is possible that similar issues occurred during this outbreak.

This case–control study found that hospital admission was independently associated with measles infection/transmission. However, it is difficult to distinguish between patients who were exposed in emergency departments and patients who were exposed in inpatient departments, as most inpatients are admitted through an emergency department. Nevertheless, inpatients would have had a longer length of stay, providing a longer duration for exposure to a measles case and possibly more time to come into contact with an infected person.

Although targeted by routine vaccination, children under five years of age remain the highest risk group for measles infection, and outbreaks continue to occur despite relatively high uptake of the MMR vaccine. However, these uptake rates are short of the 95% target recommended for attaining herd protection. As this study implies, cohorts of unvaccinated/partially vaccinated children continue to accumulate, resulting in an increased risk of measles infection and outbreaks. Consequently, children too young for routine vaccination (<14 months) do not have the protection afforded by herd immunity. Although appropriate in smaller contextual outbreaks, bringing forward the vaccination of children who were under age for the first dose of the MMR vaccine was not considered applicable in this outbreak.[8] Therefore, the continued concerted effort of healthcare professionals and the media to promote immunization is critical to reduce missed/avoided routine vaccination and meet the 95% target. Catch-up MMR immunization campaigns in children between five and 18 years have had varied

success, but lessons learned from previous campaigns should help to increase their success in the future.[23–25] It is important that these strategies, especially school MMR catch-up programmes, are given higher priority.

Healthcare settings also contribute to measles transmission, as shown in this case–control study. In order to reduce transmission, it is critical to increase measles awareness among practitioners to ensure rapid diagnosis, early isolation of cases, and implementation of enhanced infection control measures. Although not investigated in this case–control study, other studies have shown the importance of healthcare worker immunity in the reduction of transmission.[20–22] The MMR vaccination status of front-line healthcare workers was also found to be a significant issue in the Merseyside outbreak covered by this study.[26] It is recommended that evidence of immunity against measles/MMR vaccination status of front-line healthcare workers should be identified, recorded and accessible.

Strengths and limitations

Any selection bias was minimized as cases were selected at random, and over half of all confirmed cases (42/71) at the time of study took part with no refusals to participate. Controls were matched by general medical practice and age. General medical practice was used as a proxy of a participant's area of residence, and because it provided a method for rapid identification of age-matched controls. However, when using this method to match area of residence, it is possible that some participants may be registered with a general medical practice in another residential area, and therefore not be appropriately matched in terms of area of residence. Analysis of the participants' postcodes revealed that this was not an issue in this sample, and should not have affected the final analyses.

Data quality and completeness were high for both cases and controls, and this was helped by the fact that case demographics and travel status were already available through the case management system. One participant had no recorded vaccination status; as such, they were excluded from the univariate and multi-variate analyses that included this variable.

Use of a retrospective interview method meant that recall bias could have been an issue, particularly for controls, as participants were asked to recall events which may have happened up to three months prior to their interview. Attempts were made to minimize recall bias by shortening the time between presentation of illness and data collection as much as possible.

Although the study sample size met the minimum defined by the sample size calculation, it remains relatively small, explaining the wide CIs presented. Therefore, when used in isolation, the outcomes of this study should be interpreted with caution.

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None declared.

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