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Vaccine 23 (2005) 4070–4074
Vaccine
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The effectiveness of the mumps component of the MMR vaccine: a case control study

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Received 21 May 2004; accepted 22 October 2004

Abstract

In 1998/1999, an outbreak of mumps occurred among children of a religious community in North East London. A case control study was conducted to assess the effectiveness of the mumps component of the MMR vaccine. One hundred and sixty-one cases of mumps were identified and 192 controls were selected. Fifty-one percent of cases and 77% of controls had a history at least one MMR vaccination. The observed effectiveness of any MMR vaccination adjusted for age, sex and general practice was 69% (95% CI: 41–84%). This is consistent with the results of other observational studies of mumps containing vaccines, but lower than the immunogenicity of mumps vaccines reported by clinical trials. This discrepancy is because observational studies tend to underestimate vaccine effectiveness, and because immunogenicity is not necessarily an accurate biological marker of vaccine effectiveness. Two doses of vaccine were more effective (88% (95% CI: 62–96%)) than a single dose (64% (95% CI: 40–78%)). The current two-dose vaccination programme remains the best method for controlling mumps infection in the community.

Keywords: Mumps; Vaccine; Case-control

1. Introduction

Mumps is a potentially serious viral infection, the incidence of which has declined dramatically since the introduction of the MMR vaccine in October 1988. In England and Wales the number of notified cases fell from 20,713 in 1989 to 1587 in 1998 [2], and similarly dramatic declines in have followed the introduction of mumps vaccines in the US [3], Sweden [4] and Finland [5]. However, outbreaks of mumps occur where vaccination coverage is low. Mumps has re-emerged as an important infection of childhood and early adulthood as uptake of the MMR vaccine has fallen in England and Wales [2,6,7].

Between June 1998 and May 1999, an outbreak of mumps occurred in North East London due to genotype C virus, thought to have been imported from abroad [1]. As the outbreak became apparent, the local Consultant in Communicable Disease Control (CCDC) wrote to all local general practitioners (GPs) to encourage statutory notifications of clinical cases of mumps. Of the 144 cases notified, 142 were children of a single religious community and were notified by two general practices, A and B, which served this community. The community was concentrated into a relatively small geographical area and had its own schools and amenities. MMR vaccination coverage was low, between 67 and 86%. A case control study was conducted to identify unreported cases and to assess the effectiveness of the mumps component of the MMR vaccine.

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doi:10.1016/j.vaccine.2004.10.020

2. Methods

2.1. Selection of cases and controls

A case was defined as a clinical or laboratory diagnosis of mumps with date of onset from 18 June 1998 to 2 May 1999. All cases in children aged between 1 and 18 years old from the religious community were included. Cases were identified in three ways. Firstly from statutory notifications of mumps from general practices A and B to the local CCDC. Secondly from searches of the electronic practice lists. Both practices used the EMIS system and patients' notes were updated following all consultations. These were searched for relevant diagnoses using the term "mumps". The clinical records of the cases retrieved were checked by hand to establish whether they fitted the case definition. Finally cases were identified from verbal reports by members of the community. Membership of the community was ascertained by religious practice as recorded in general practice records, by using surname, or from school attended. For cases that were notified, laboratory testing of oral fluid for mumps IgM antibody and mumps RNA was offered at the Enteric, Respiratory and Neurological Virus Laboratory (ERNVL).

Controls were selected from children of the same community registered with practices A and B. Membership of the community was ascertained as for cases. All children in the same age range as cases were eligible for inclusion. A stratified random sample of these children was taken from the electronic practice lists, using random number tables, to match the age and sex profile of cases.

2.2. Data collection

Details of the age, sex, school and vaccination status of cases and controls, and clinical details about cases were obtained from practice records. Vaccination histories of cases and controls were cross-checked with the local health authority child health immunisation database. Laboratory results were obtained from the ERNVL.

2.3. Statistical methods

Epi Info version 6 was used for data entry, cleaning and descriptive analysis. Data were then transferred into Stata version 7 to calculate an odds ratio (OR) for cases having received MMR vaccination (one or two doses) compared to controls, and to take into account the effect of potential confounding factors: age, sex and GP practice. Vaccine effectiveness was determined from 100 X (1-OR).

3. Results

A total of 161 cases aged between 1 and 18 years were identified with dates of onset during the outbreak period (Fig. 1). One hundred and forty-two cases were notified by general practices A and B, 12 were identified through electronic searches of the practice lists, and seven were reported by parents. Forty-three (30.3%) of the notified cases were confirmed in the laboratory by IgM radio immunoassay, detection of mumps RNA by PCR, or both. Six cases (3.7%) of complications associated with mumps were recorded: two

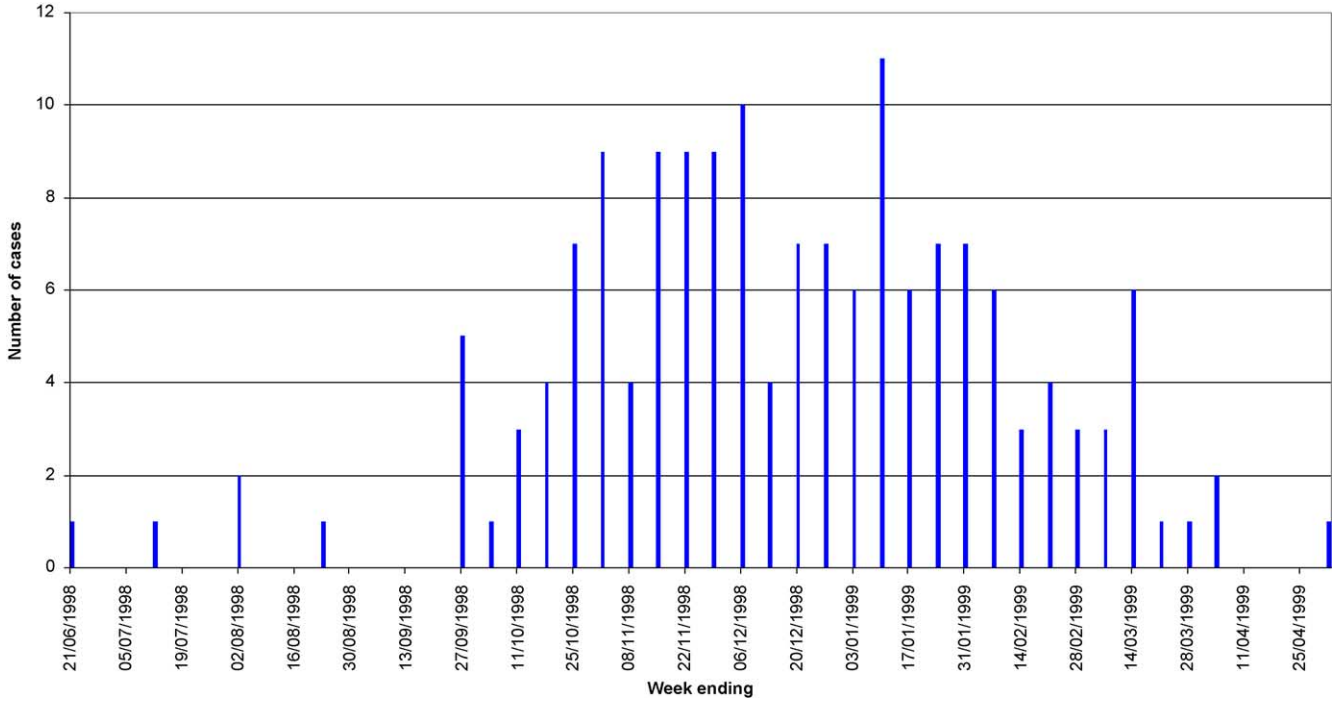

Fig. 1. Epidemic curve for the outbreak. *Note*: One case had no date of onset specified, although the illness occurred during the outbreak period.

of meningism, two of orchiditis, one of prolonged parotiditis and one of abdominal pain.

One hundred and ninety-two controls were selected at random from the electronic lists of the two practices. Vaccination status was available for 156 (96.9%) cases and 175 (91.1%) controls. Further analysis was limited to these cases. Membership of the religious community was ascertained for 96 cases and controls from computerised or paper records or discussion with the GP, 234 from surname, and one from school attended. Cases and controls were similar to cases in terms of age, sex and the proportion registered with each practice: at the end of the outbreak, the mean ages of cases and controls were 9.4 (S.D. = 3.4) and 9.7 (S.D. = 3.8) years, respectively ($p = 0.41$); 87 (56%) cases and 92 (53%) controls were male ($p = 0.56$); and 78 (50%) cases and 84 (48%) of controls were registered with practice A ($p = 0.72$). Seventy-nine (51%) cases and 134 (77%) controls had a history of at least one MMR vaccination, at least 1 month prior to onset of illness in cases. Five cases and 22 controls had a history of two MMR vaccinations.

The crude OR for cases having received any MMR vaccination compared to controls was 0.31 (95% CI: 0.20–0.50) ($p < 0.00001$), giving a crude vaccine effectiveness of 69% (95% CI: 50–80%). The OR of cases compared to controls having received any MMR vaccination was higher for males than females: 0.39 (95% CI: 0.20–0.78) compared to 0.25 (95% CI: 0.14–0.50), and higher for children registered with practice A than practice B: 0.49 (95% CI: 0.24–0.98) compared to 0.20 (95% CI: 0.10–0.39). This latter interaction verged on significance ($p = 0.08$).

After adjustment for age, sex and general practice the effectiveness of any MMR vaccination was 69% (95% CI: 41–84%). Considering just cases that were confirmed by the laboratory, the adjusted effectiveness of any MMR vaccination was 65% (95% CI: 25–84%). The effectiveness of two doses of MMR was 88% (95% CI: 62–96%), higher than that of a single dose (64% (95% CI: 40–78%)), although small numbers limited the significance of this finding.

4. Discussion

The mumps component of the MMR vaccine used in the UK, which contains the Jeryl Lyn strain, is generally accepted to confer protection to around 90% of recipients [8]. This figure is based mainly on trials that have examined the immunogenicity of mumps vaccines [9–12]. Observational studies conducted during mumps outbreaks have generally found the effectiveness of mumps vaccines to be lower. Our observed vaccine effectiveness of 64% for a single dose of MMR is similar to the results of other observational studies of vaccines containing the Jeryl Lynn and Urabe Am9 strains of mumps virus (see Table 1 [13–29]).

There are several possible explanations for the discrepancy between vaccine effectiveness reported by observational studies and immunogenicity reported by clinical trials. On the one hand, vaccine effectiveness may be underestimated by observational studies. Outbreaks of mumps are more likely to occur when poorly protective vaccines have been used, and observational studies are liable to a number of methodological weaknesses that limit the validity of their results, as discussed below. On the other hand, the protection afforded by vaccination may be overestimated by pre-licensure trials, which have often been uncontrolled and of poor methodology, and immunogenicity may not correlate fully with clinical protection. Vaccines may also be less effective under field conditions due to problems with distribution, storage or administration—for example a failure to correctly maintain the cold chain.

There are four key methodological considerations for observational studies of vaccine effectiveness: case definition, ascertainment of cases and vaccination status, and similarity of cases and controls [30]. The clinical diagnosis of mumps lacks specificity and sensitivity. Where mumps is rare, clinicians and parents unfamiliar with its presentation may report illnesses mimicking the clinical features of mumps. This can lead to underestimation of vaccine effectiveness as these cases fall disproportionately into the vaccinated group since mumps vaccination cannot protect against other conditions. This was not a major concern in our study because the estimates of vaccine effectiveness based on clinical diagnosis and laboratory confirmation were similar.

Conversely, genuine cases of mumps will be missed. Some will have a sub-clinical presentation, and others will go unreported: there is considerable underreporting of infectious diseases through statutory notification systems. This should not affect estimates of vaccine effectiveness unless a different proportion of cases are missed in vaccinated and unvaccinated groups. This potential bias was minimised in our study by active case finding in each practice. However, children who were unregistered with a GP would not have consulted with mumps and would not have been vaccinated, which would have lead to underestimation of vaccine effectiveness. Conversely, observer bias may have produced better case ascertainment in the unvaccinated group if clinicians were more willing to make a diagnosis of mumps in children they knew to be unvaccinated, which would have lead to overestimation of vaccine effectiveness.

We used two sources of information to improve accuracy of vaccination history of cases and controls and limit bias due to misclassification of vaccination status. In addition, there is no reason to believe that vaccinations were systematically recorded better or worse in the case and control groups. Vaccine storage and administration was investigated as part of the outbreak control, but no failures of the cold chain or problems with vaccination technique were identified.

A final concern with the validity of our results is whether cases and controls had an equal risk of exposure to infection. Firstly, selection of controls was not confined to those who were known to be susceptible to mumps prior to this outbreak. Controls who had previous mumps infection would have acquired immunity without vaccination, which could have lead

Table 1
Effectiveness of mumps vaccines in other field evaluations

Setting and study population	Study design	Case definition	Case finding	Selection of controls	Ascertainment of vaccination status	Attack rates and vaccine efficacy
867 children, aged 1–13 years, exposed to mumps over a 4–9-month period, in Philadelphia, US, 1965–1966 [13]	Prospective cohort	Laboratory confirmation of mumps	Children visited twice weekly and assessed for symptoms	From 505 children who did not develop mumps	All children were initially seronegative, 362 were vaccinated	2/100 vaccinated children and 115/721 unvaccinated pupils developed mumps: VE = 97% (87–99%)
121 cases in a kindergarden with 899 children in New York State, US, 1973 [14]. Mumps vaccine coverage <20%	Retrospective cohort					6/178 vaccinated pupils and 115/721 unvaccinated pupils developed mumps: VE = 79% (53–91%)
84 cases in six schools with 757 pupils in Ontario, Canada, 1977 [15]	Retrospective cohort	Parental report of symptoms and confirmation by clinical diagnosis	Active contact with parents of all children	All remaining consenting children	Parental questionnaire	8/200 vaccinated and 508 unvaccinated pupils developed mumps VE = 73% (46–87%)
62 cases in a school with 500 pupils in Ohio, US, 1981 [16]. Mumps vaccine coverage 73%	Retrospective cohort	Parotid swelling for one or more days	Active follow up of all absent pupils	All remaining consenting children	School immunisation records and parental questionnaire	34/393 vaccinated and 28/88 unvaccinated pupils developed mumps: VE = 73% (58–83%)
110 cases in a school with 357 pupils in Ohio, US, 1982 [17]	Retrospective cohort	Parotid swelling for two or more days	Diagnoses made by school nurse and active contact with parents of all children	All remaining consenting children	School immunisation records and parental questionnaire	19/128 vaccinated and 70/142 unvaccinated pupils developed mumps: VE = 70% (51–81%)
25 cases in sixth grade (165 pupils) of school in New Jersey, US, 1983 [18]	Retrospective cohort	Parotid swelling for two or more days	Reports from schools	All remaining children	School vaccination records	5/122 vaccinated and 19/43 unvaccinated pupils developed mumps: VE = 91% (77–96%)
332 cases in a school with 1764 pupils in Tennessee, US, 1986 [19]. Mumps vaccine coverage in the county as a whole was >95% but lower in the affected school	Case control	Parotid swelling	Active contact with parents of all children	Stratified random sample of remaining children	Medical records	31/184 cases and 97/201 controls had a history of vaccination: VE = 78% (65–86%)
138 cases in three schools with 1721 pupils in Kansas, US, 1988–1989 [20]. Mumps vaccine coverage 99%	Retrospective cohort	Parotid swelling	Reports from local clinicians, review of absentees and questionnaire for pupils	All remaining children	School immunisation records with some verification from medical records	135/1713 vaccinated pupils and 3/8 unvaccinated pupils developed mumps: VE = 83% (57–94%)
54 cases in school with 318 pupils in Texas, US, 1990 [21]. Mumps vaccine coverage 98%	Retrospective cohort	Parotid swelling for two or more days	Questionnaire for pupils	All remaining consenting children	School immunisation records with verification from medical records	53/299 vaccinated pupils developed mumps
68 cases in school with 1460 pupils school with Tennessee, US, 1991 [22]. Mumps vaccine coverage 98%	Retrospective cohort	Parotid swelling with acute onset and lasting two or more days	Active contact with local clinicians	All remaining consenting children	School immunisation records with some verification from medical records	67/1090 vaccinated pupils and 1/26 unvaccinated pupils developed mumps
Community outbreak. Geneva, Switzerland, 1991 [23]. Mumps vaccine coverage 80%	Prospective cohort		63 secondary cases observed in household contacts of 283 primary cases	All other household contacts of the primary cases		VE by strain: Jeryl Lynn 62% (0–85)%; Urabe 73% (42–88%)
88 confirmed cases in Switzerland, 1992–1993 [24]. Overall mumps vaccine coverage 61%	Case control	Viral isolation	Salivary swabs for laboratory diagnosis taken from 102 patients aged 2–16 years presenting with parotiditis at 2 paediatric practices over 15 months	92 children registered with the same paediatric practices	Medical records	3/16 cases and 18/54 controls had a history of vaccination. VE of Jeryl Lynn strain: 54% (−108–91%)
216 cases in 19 schools in Toledo, Spain, 1993 [25]	Retrospective cohort	Clinical diagnosis		All remaining 4059 children		VE = 76% (66–87%)
10 classes with 205 children in a school in Geneva, Switzerland, 1994 [26]	Retrospective cohort	Clinical diagnosis	63 secondary cases observed following a single primary case in each class	All remaining 132 children		VE by strain: Jeryl Lynn 65% (11–86)%; Urabe 75% (36–91%)
66 cases in a cohort of 165 children aged 5–13 in a small community in a rural area of Switzerland [27]. Mumps vaccine coverage >95%	Prospective cohort	Clinical diagnosis or viral isolation from culture	Questionnaire for parents of all children	All remaining children	Parental questionnaire	VE by strain: Jeryl-Lynn 78% (64–82%); Urabe 87% (76–94%)
283 cases among children in an urban area of Spain, 1996 [28]	Retrospective cohort	Clinical diagnosis	Infectious disease register	Other children selected from the local population census	School vaccination records, vaccination cards and health register	VE = 46% (0–84%)
Outbreak of mumps associated with attendance at a rave party in Canada, 1997 [29]	Case control	Clinical diagnosis			Self reported vaccination status	VE = 80% (29–96%)

to underestimation of vaccine effectiveness. Secondly, the outbreak lasted for over 10 months, and controls were therefore collectively exposed to infection for longer than cases. This was not taken into account in the analysis and could also have lead to underestimation of vaccine effectiveness. Finally, we had no information about potential confounding factors other than age, sex and general practice that may have influenced the risk of infection and the vaccination status of cases and controls. It was not possible to accurately define our population because the religious community did not have a clearly defined census category or geographical district for enumeration. We made a number of checks to ensure that both cases and controls were drawn from this community, although the use of names to ascertain membership of ethnic and religious groups is subject to inaccuracies [31]. However, it was not possible to determine whether cases and controls were drawn from the same parts of the community or whether they were drawn from different residential areas or distinct groups with different levels of herd immunity and different behaviours.

Our study found that mumps vaccine was effective at preventing mumps. Vaccine effectiveness was lower than immunogenicity reported by clinical trials. This discrepancy is expected because observational studies tend to underestimate vaccine effectiveness, and because immunogenicity is not necessarily an accurate biological marker of vaccine effectiveness. Two doses of vaccine provided greater protection than a single dose, and this emphasises the need to have high coverage of a two-dose programme to prevent mumps outbreaks in the future.

Acknowledgements

Dr. Bernard Cohen, HPA-CDSC, 61 Colindale Avenue, London, NW9 5EQ. All staff of the two General Practices who contributed data to the study.

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