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An outbreak of mumps with genetic strain variation in a highly vaccinated student population in Scotland

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SUMMARY

An outbreak of mumps within a student population in Scotland was investigated to assess the effect of previous vaccination on infection and clinical presentation, and any genotypic variation. Of the 341 cases, 79% were aged 18–24. Vaccination status was available for 278 cases of whom 84% had received at least one dose of mumps containing vaccine and 62% had received two. The complication rate was 5·3% (mainly orchitis), and 1·2% were admitted to hospital. Genetic sequencing of mumps virus isolated from cases across Scotland classified 97% of the samples as genotype G. Two distinct clusters of genotype G were identified, one circulating before the outbreak and the other thereafter, suggesting the virus that caused this outbreak was genetically different from the previously circulating virus. Whilst the poor vaccine effectiveness we found may be due to waning immunity over time, a contributing factor may be that the current mumps vaccine is less effective against some genotypes. Although the general benefits of the measles–mumps–rubella (MMR) vaccine should continue to be promoted, there may be value in reassessing the UK vaccination schedule and the current mumps component of the MMR vaccine.

Key words: Community outbreaks, infectious disease epidemiology, MMR vaccination, mumps, viral genotyping.

INTRODUCTION

Mumps is a potentially serious viral infection with complications of orchitis, aseptic meningitis, oopheritis, pancreatitis and encephalitis [1, 2]. Mumps was an extremely common childhood disease in the UK until routine immunisation with measles–mumps–rubella (MMR) vaccine was introduced in 1988 [3]. This was initially given as a single dose for children aged 12–15 months of age. In 1996 a two dose schedule was introduced with the second dose given preschool [3]. A single dose of the MMR vaccine used in the UK, which contains the Jeryl Lynn mumps strain, has been reported to confer between 61 and 91% protection [3, 4]. Observational studies conducted during

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mumps outbreaks have generally found the effectiveness of mumps vaccine to be closer to 64% for a single dose and 88% for two doses [4].

MMR uptake in Scotland is high, with 93% of children receiving two doses of vaccine by the age of five [5]. Historically, Scotland has maintained a high vaccine uptake: the average uptake of two MMR vaccines for children born between 1992 and 1997 ranges between 85·7 and 90·8% [5].

Despite a national MMR vaccination programme, outbreaks of mumps continue to occur. Large outbreaks occurred in university students in Scotland in 2004, 2007, and 2009, with a smaller outbreak in 2012 [6, 7]. However, these were predominantly in populations in which a significant proportion of individuals were either unvaccinated or partially vaccinated with a mumps virus containing vaccine [6–8].

Edinburgh and the surrounding area in south east Scotland comprise Lothian (approximately 850 000 people) [9]. There are four universities in Edinburgh, and the area has a large multi-cultural student population of over 60 000 [10]. University A is one of the most internationally diversified universities in the UK, with 36% of the campus of 9000 coming from outside the UK.

During the academic year 2014/2015 a large outbreak of mumps occurred in Lothian. The outbreak was identified in early October 2014, when a general practitioner (GP) reported a higher than expected number of cases of mumps in students from one university campus (University A), with early cases largely occurring in students residing in halls of residence. Over time, the infection spread to students across the other three universities in Edinburgh and subsequently outwith the student population.

We describe the epidemiology of the outbreak and assess the effect of prior MMR vaccination on epidemiology and complication rate. Through use of a laboratory report-based, national surveillance system we also present phylogenetic analysis of the mumps virus.

METHODS

Epidemiology

Mumps is a statutory notifiable disease in Scotland [11]. Local public health departments are notified of laboratory confirmed cases of mumps via electronic laboratory surveillance systems and clinical notification is received from GPs. The case definition included all notifications of mumps, both laboratory confirmed and clinical diagnoses, from any resident within Lothian. Case numbers were reported during the outbreak period from week 40, 2014, until week 26, 2015.

From October 2014 enhanced surveillance of mumps across Lothian was carried out. This included:

i. communications to GPs to encourage notification of all cases of mumps
ii. collection of epidemiological data for all cases
iii. review of Scottish Immunisation and Recall System, individual patient records and telephone calls to general practices to obtain MMR status.
iv. visit to university general practices to review records and collect details of clinical presentation
v. review of hospital data to identify the number of cases who required hospitalisation due to a complication of mumps.

Data were collated and analysed using Microsoft Excel. Further statistical analysis of data was performed using SPSS Statistics (version 23·0, Armonk, NY) to assess the relationship between hospitalisation, mumps complication rates and vaccination status.

Virology

Pharyngeal swab samples collected from mumps cases across Scotland between September 2012 and May 2015, i.e. before and during the outbreak, were sent to the East of Scotland Specialist Virology Laboratory at the Royal Infirmary of Edinburgh for genotyping and viral characterisation. Of the 84 mumps-positive swab samples received, 38 came from cases, which occurred during the outbreak.

Viral nucleic acid was extracted from each sample using the NucliSENS® easyMag® platform (Biomerieux®, Marcy-l'Étoile, France). The presence of mumps RNA was studied by an in-house real-time polymerase chain reaction (PCR), which amplifies a fragment of the F gene following the Uchida *et al.* method [12].

Genotyping of positive samples was conducted through a reverse transcriptase-PCR assay using the OneStep RT-PCR Kit (Qiagen®, Venlo, Netherlands). This assay was designed to amplify the small hydrophobic (SH) gene, targeting the complete coding region of the SH gene, following the WHO recommendations for characterisation of mumps virus (MuV) diversity [12–14].

The amplicons were sequenced using the BigDye® Terminator v3·1 Cycle Sequencing Kit (ThermoFisher Scientific, Massachusetts, USA) and sent to Edinburgh Genomics at the University of Edinburgh to be read by a ABI 3730 capillary Sanger sequencing instrument.

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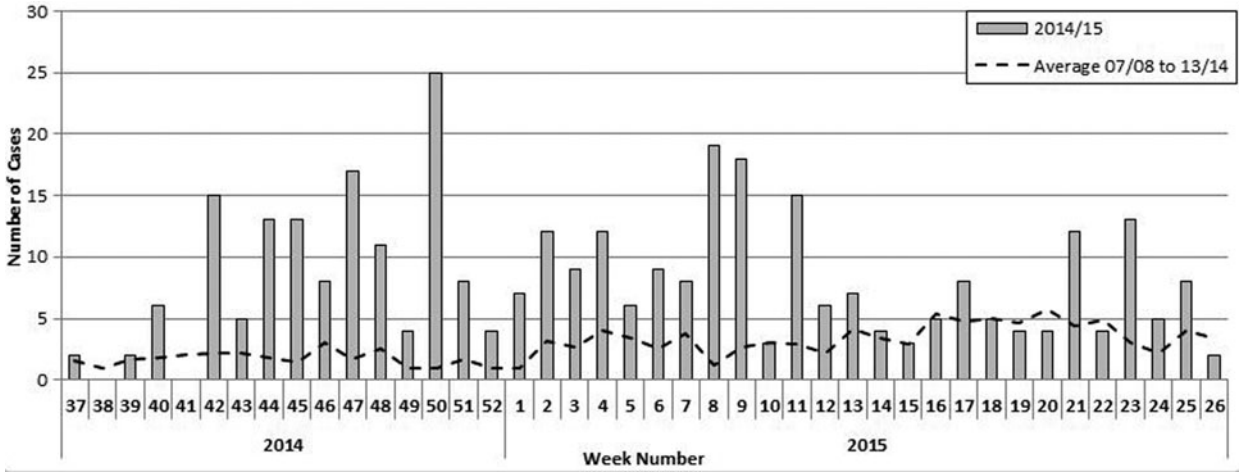

Fig. 1. Epidemic curve of mumps outbreak in Lothian, Scotland, October 2014–June 2015 ($n = 341$).

Primers used to identify the SH gene were: forward SH1, 5′ AGTAGTGTCGATGATCTCAT 3′ and reverse SH2, 5′ GCTCAAGCCTTGATCATTGA 3′ resulting in an amplicon of 639 nucleotides [14]. Of the total 84 samples only 62 SH genes had enough gene RNA for sequencing alignment.

The sequences were aligned to reference mumps virus type C [AY669145] using the Simmonic Sequence Editor V1·4 software. Following the MEGA 7·0 software recommendation, the phylogenetic tree of the coding region of the SH gene (316 nt) was obtained using the Hasegawa-Kishino-Yano model, Maximum-likehood (ML) method and with bootstrap test [15, 16]. Sequences were analysed and compared with genotypes A [GU980052], B [AB000388], C [JQ945268], D [JQ034452], F [EU780221], G [AF280799], H [JQ945273], I [AY309060], J [JQ945271], K [JQ945270], L [AB105483], N [AY380077] and Jeryl Lynn vaccine JL [AF338106] obtained from the mumps virus nomenclature update [13].

RESULTS

The outbreak spanned 39 weeks from week 40, 2014 until week 26, 2015 (Fig. 1 illustrates the epidemic curve). Background average weekly numbers of mumps notifications in Lothian from 2007/2008 to 2013/2014 (years April to end March) are included in Figure 1.

Of the 341 cases clinically notified during the outbreak, 93% were laboratory confirmed. The majority of cases were in the student-aged population, with 60·7% being aged 18–22 and a slight male predominance (54% male). In total, 162 cases (47·5%) were confirmed to be students. In University A where the outbreak began, approximately 40% of cases in the cluster were resident in student halls. Despite the international nature of the student population of Edinburgh, we estimate that only 26 (7·6%) of the 341 cases in this outbreak were in individuals from overseas, all of whom were students. Within the context of this outbreak investigation the vaccination status of these individuals, or previous exposure to mumps could not be confirmed reliably.

MMR status was obtained for 278 of the 341 cases; 172 (61·9%) of these were fully immunised against mumps (Table 1). Analysis of MMR status by age highlights that 83·7% of those cases who were fully immunised with two doses of MMR were aged between 18 and 24. In total, 265 cases in this outbreak would have been eligible for two MMR vaccines in childhood: 166 of them (62·7%) received two.

Clinical case files were reviewed for 88 cases registered at the health service practices of two Edinburgh universities. This information highlighted that cases generally reported a mild pattern of illness with just five cases (5·7%) having a recognised complication of mumps documented, all of which were orchitis. None required hospital admission. Forty eight of the 88 cases (54·6%) were fully immunised with two MMR vaccines. None of those cases who were diagnosed with complications of mumps had been fully vaccinated: two cases had received one MMR, two had received no MMR and for one case the immunisation status was unknown. Twenty three of the cases (26·1%) had unknown vaccination history, due predominantly to the international nature of the student population.

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Table 1. *Measles–mumps–rubella (MMR) vaccination status in relation to age of mumps cases during an outbreak in Lothian, Scotland, October 2014–June 2015 (n = 341)*

	Age in years					
MMR status	0–12	13–17	18–24	25–34	35+	Total (%)
Not vaccinated	0	1	14	11	17	43 (12·6)
One dose	2	1	35	25	0	63 (18·5)
Two doses	10	12	144	6	0	172 (50·4)
Unknown	0	0	46	13	4	63 (18·5)
From Overseas	0	0	23	3	0	26
GP does not have immunisation record	0	0	8	8	1	17
GP unknown	0	0	3	1	0	4
No longer registered at GP	0	0	10	1	1	12
Unknown	0	0	2	0	2	4
Total	12	14	239	55	21	341

Table 2. *Severity of clinical presentation (hospitalisation) and measles–mumps–rubella (MMR) status of mumps cases during an outbreak in Lothian, Scotland, October 2014–June 2015 (n = 341)*

	Severity of clinical presentation as measured by type of healthcare used				
MMR Status	Primary care (GP) only	A&E	Hospital outpatient	Hospital admission	Total
Not vaccinated	40	0	2	1	43
One dose	60	3	0	0	63
Two doses	158	8	3	3	172
Unknown	51	9	3	0	63
Total	309	20[a]	8[b]	4	341

A&E, accident and emergency department.
[a] Of the 20 people seen in A&E, 10 presented for their initial diagnosis without any complications, one had been diagnosed in primary care but attended A&E for reassurance and nine had orchitis.
[b] All eight outpatient appointments were to Ear, Nose and Throat or Maxillofacial services, all for uncomplicated facial swelling, and for all the initial diagnosis was made there.

Hospital records were reviewed for all 341 cases to identify the number of cases who were hospitalised during their mumps illness (Table 2). Four cases, all of them laboratory confirmed, were admitted to hospital. Of these, three were due to mumps complications (one with aseptic meningitis, one with mild meningism, and one patient who had both mild pancreatitis and epididymo-orchitis) and one where the association was less clear (possible nephritis). Of the four admissions, three were fully vaccinated with two doses of MMR and one (with aseptic meningitis) had received no mumps containing vaccine. A further 28 cases attended secondary care. Twenty attended the accident and emergency (A&E) department; for ten this was their initial (uncomplicated) presentation. A further nine males presented to A&E with orchitis, not requiring hospital admission. A further eight cases were referred to ear, nose and throat or maxillofacial services as outpatients, all for uncomplicated facial swelling, and all diagnosed with mumps in the outpatients setting.

Out of the 62 mumps samples suitable for genotyping (MF522080 – MF522141), 60 (97%) of the samples were classified as genotype G while one was classified as genotype D and the other genotype H. The nucleotide identity between the sequences of the two clusters was 94·98%. The phylogenetic tree shows two distinct clusters of genotype G, one circulating before September 2014 and the other thereafter (Fig. 2). This suggests that the virus, which caused the outbreak was slightly genetically different from the previously circulating virus.

DISCUSSION

We report a large outbreak of mumps in a highly vaccinated population. These results can be considered to have a high level of accuracy reflecting the number of

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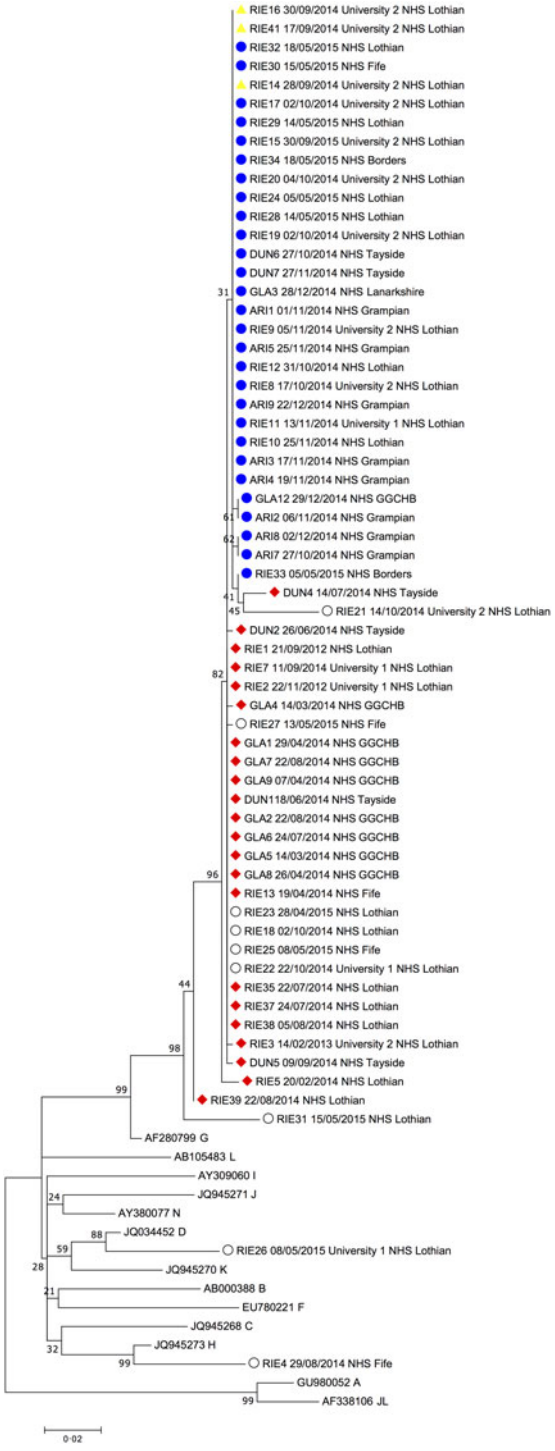

Fig. 2. Phylogenetic analysis for the SH gene (316 nt) of mumps strains from patients in Scotland 2012–2015. Bootstrap values (%) are shown at each node. Scale bar indicates the number of substitutions per nucleotide position. ● Outbreak strain identified during the outbreak. ○ Different strain detected during the outbreak. △ Outbreak strain but identified prior to the official start date of the outbreak. ◆ Pre-outbreak mumps virus circulating.

methods used to collect data. However, our report is confined to a single outbreak investigation, and with small numbers of particular outcomes, statistical analysis was not possible. A further limitation of our investigation is that we were not able to confirm the vaccination status of cases born outside the UK. As all these individuals were recorded as having 'unknown' vaccination status, the true number of vaccinated cases would be higher than that reported.

The complication rate observed here is low in comparison with studies from the pre-vaccine era [3]. Our total complication rate was 5·3% (18 of 341 cases). The complication rate in males was 9%, mostly orchitis. This finding is in accordance with other mumps outbreaks where males tend to experience more complications than their female equivalents [17]. From enhanced surveillance of over 15 000 patients in the post-vaccine era, Yung *et al.* report orchitis as the most common complication at 6·1% [18]. Yung *et al.* also report hospitalisation rates of between 2·9% and 6·1%; with vaccination with one dose of MMR having a protective effect in reducing the risk of hospitalisation [18]. In our study the hospitalisation rate was 1·2% (four cases, $n = 341$) but if the patient with nephritis is excluded, the hospitalisation rate due to mumps falls to 0·88% (3/341). Nevertheless there was appreciable secondary care impact with 9·4% (32 of 341 cases) cases attending secondary care.

The lower than expected complication rates observed in this outbreak may reflect more complete case ascertainment as a result of clinical notifications. However, it is more likely that our data support Yung *et al.*' view that vaccination against mumps can lead to a shift towards milder forms of the disease [18]. Our study is also consistent with a recent study in the Netherlands, which found that disease was less severe in fully vaccinated individuals compared with unvaccinated individuals; measured by the proportion of cases with orchitis and bilateral parotitis in each group [19].

Outbreaks of mumps in vaccinated populations, in particular young adults/students, have been reported previously [20] with several contributing factors proposed. The effectiveness of mumps vaccination may wane over time [21] and this is likely to have contributed to this outbreak. A vaccine effectiveness study of a large mumps outbreak in England during 2004/2005, also involving predominantly a young adult population, found that vaccine effectiveness declined markedly with time; falling from 95% to 86% for

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two doses 10 years after vaccination [22]. In contrast, an Irish study found no evidence of waning immunity in mumps specific IgG positive individuals with IgG levels greater in those in older age groups, however, more time for boosting from circulating mumps virus in older individuals may account for this [23]. A large proportion of the student cases in this outbreak were from the UK where the childhood immunisation schedule recommends that the second dose of MMR vaccine be given at age 3 years 4 months (or soon after) [3]. Consequently, by the time fully vaccinated young adults attend higher education aged 18+ years it may be >10 years since the time of their second vaccination. In several European countries it is recommended that the second dose of MMR vaccine is given later in childhood [24].

A third dose of MMR vaccine may aid control of mumps outbreaks among populations with pre-existing high vaccine coverage [25]. A French study concluded that the effectiveness of mumps vaccine wanes with time and proposed the introduction of a targeted third dose in outbreak settings for individuals whose last dose was more than 10 years ago [21]. A third dose was used in three schools in north-eastern USA during a massive outbreak of 1500 cases [25]. Subsequently, the attack rate in those school populations declined from 4·9% pre-intervention to 0·13% after. Another option is of routine offer of a third dose of MMR for those entering higher education institutions. However, there is little published evidence to support this approach.

The majority of cases in this outbreak were caused by genotype G. This finding is consistent with the fact that genotype G is the predominant circulating mumps virus in the UK since the mumps resurgence in 2004 [26]. In our analyses, two distinct clusters of genotype G can be identified; one before September 2014 and one from after the outbreak started. This may suggest that a change occurred within the circulating mumps virus, which decreased the neutralising capacity of vaccine induced antibodies and increased the susceptibility within the population. Genetic differences between vaccine strains and circulating wild-type strains have been proposed as a factor for outbreaks in vaccinated populations and the results from genetic studies and animal models support this [27]. Comparisons of the antigenic regions of the mumps virus vaccine strains with wild-type mumps virus observed that the Jeryl Lynn strain, found in the MMR vaccines in use in the UK, was the most genetically dissimilar from the wild type strains [28]. Furthermore, historically isolated wild-type viruses are neutralised more effectively by antibodies to vaccine strains compared with currently circulating viruses, suggesting antigenic changes have occurred in mumps viruses over time [29]. It is clear further research is required to fully elucidate the role of genetic differences between vaccine and wild type strains in infection and whether they are a major driver of mumps outbreaks. We suggest that the haemagglutinin-neuraminidase (HN) gene should be sequenced for a more complete resolution.

We conclude that while the effectiveness of the current mumps component of the MMR vaccine in preventing infection may wane over time, and may be less effective against some mumps strains, two doses of vaccine seems to decrease the likelihood of complications. It should also be highlighted that MMR vaccine is extremely protective against measles and rubella (there have been no laboratory-confirmed cases of rubella in Scotland between 2014 and 2016). Students enrolling in university should be encouraged to have documentation of two doses of MMR vaccine. Evidence of the potential effectiveness and cost effectiveness of a third dose to control an outbreak should be accrued.

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DECLARATION OF INTEREST

None.

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