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Research

Mumps outbreak in an unimmunized population – Luanshya District, Copperbelt Province, Zambia, 2015

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Abstract

Introduction: Mumps is a vaccine-preventable viral disease that may cause deafness, orchitis, encephalitis or death. However, mumps vaccine is not included in Zambia's Expanded Program for Immunization. In January 2015, Integrated Disease Surveillance and Response data revealed an increase in reported mumps cases in Luanshya District. We investigated to confirm the etiology and generate epidemiological data on mumps in Zambia. **Methods:** We conducted active case finding, examined possible case-patients, and administered a standard questionnaire. A suspected mumps case was defined as acute onset of salivary gland swelling in a Luanshya resident during January - June 2015. Eight case-patients provided serum samples to test for mumps-specific immunoglobulin IgM, and buccal swabs to test for mumps viral RNA by RT-PCR, and genotyping of mumps virus at the Centers for Disease Control and Prevention, Atlanta, Georgia, USA. **Results:** From January – June 2015, a total of 283 mumps cases were reported in Luanshya, peaking in April (71 cases) and clustering (81%) in two townships. Of 72 suspected case-patients interviewed, 81% were aged < 15 years (29%, 1 - 4 years) and 61% were female. Common clinical characteristics were buccal tenderness (29%) and fever > 37.5ºC (29%). Mumps virus genotype D was confirmed in five case-patients who tested positive by RT-PCR; six case-patients were sero-positive for anti-mumps IgM antibodies (total seven lab-confirmed cases). **Conclusion:** Our findings represent the first reported epidemiologic description of mumps in Zambia. While the epidemiology is consistent with prior descriptions of mumps in unimmunized populations and no serious complications arose, this report provides data to inform policy discussions regarding mumps vaccination in Zambia.

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Introduction

Mumps is a vaccine preventable viral disease characterised by several days of fever, headache, myalgia, and loss of appetite, followed by acute onset of unilateral or bilateral tenderness of the parotid or other salivary glands [1]. Additional complications may include deafness, orchitis, encephalitis or death [2, 3]. The incubation period ranges from 12-25 days [4] and mumps is asymptomatic in one-third of cases [2]. In unvaccinated populations, attack rates are highest (25 - 50%) among children aged 5 - 9 years [5]. There are few published data on mumps epidemiology in Africa; however, a 2012 outbreak in Marashda, Egypt resulted in more than 3,500 case reported in schoolchildren [6]. Although published reports are uncommon, the World Health Organization (WHO) vaccine-preventable diseases monitoring system 2016 global summary documented mumps cases from West Africa, including Burkina Faso (8,090 cases in 2013), Equatorial Guinea (2,350 cases in 2012) and Ghana (3,780 in 2011) and from Swaziland in southern Africa, with 14,375 cases reported between 2010 and 2011 [7, 8]. Mumps vaccine is typically administered as a combination vaccine for measles, mumps, and rubella (MMR). It is recommended that children receive two doses of MMR: one at age 12 - 18 months and another at age 4-6 years [3, 4, 9]. Mumps vaccination is currently not included in Zambia's Expanded Program for Immunization (EPI). Although mumps is not a notifiable disease in Zambia, cases are sometimes reported through the Integrated Disease Surveillance and Response (IDSR) system from health facilities. In 2014, over 2,170 mumps were reported throughout Zambia through IDSR [8]. Mumps reporting has been inconsistent, and there are no published reports on mumps epidemiology in Zambia. A review of IDSR data in April 2015 revealed an apparent increase in reported mumps cases in Luanshya District of Copperbelt Province, with 66 cases reported from 19 – 26 April, 2015, well in excess of the average of eight cases per month. On 7 May, 2015, a Field Epidemiology Training Program (FETP) resident based at Zambia's Tropical Disease Research Centre (TDRC) informed the Provincial Medical Office (PMO) and Ministry of Health (MoH) of the increase in cases. We investigated the outbreak to confirm the etiology and gather epidemiologic data.

Methods

Setting

The outbreak occurred in Luanshya District, located approximately 35 kilometres from the city of Ndola, the administrative capital of Copperbelt Province, Zambia. Luanshya District covers an area of 935 square kilometres with a population of 171,000 [10]. Luanshya is an urban district in Copperbelt province with an economy supported by mining.

Public Health response

We instituted and trained mumps response teams at four health centres. The outbreak response teams were coordinated by the principal investigator and comprised a clinician, an environmental health technologist and a nurse. The team was responsible for active case identification, reporting and community sensitisation. Mumps surveillance was enhanced by providing a standard line list and questionnaire to clinicians at each facility as well as providing air-time for mobile phone communication.

Operational definitions

We defined a suspected mumps case as acute onset of salivary gland swelling in a Luanshya resident during the period January - June 2015. A probable case was defined as a suspect case epidemiologically linked to another clinical compatible case but without laboratory confirmation. A confirmed case was defined as a probable or suspect case in a patient with serum positive for anti-mumps immunoglobulin M (IgM) antibody or by mumps real-time reverse transcription polymerase chain reaction (RT-PCR).

Data collection

From January-April 2015, we retrospectively identified cases by reviewing aggregated IDSR data reported from health facilities in Luanshya. Socio-demographic and health status data reported in the IDSR included age, gender, place of residence, date of symptom onset, immunization status and disease outcome. We selected four health centers with the highest number of reported cases in IDSR in which to conduct active case finding: Mikomfwa Health Centre, Roan Section 9 and Kawama Clinics, and Roan General Hospital. We examined possible cases and administered a standard questionnaire at these centers during May through June 2015. We collected information on exposure history, clinical symptoms and case management, in addition to demographic variables. Case-patients who had fever were tested for malaria using a rapid diagnostic test (RDT).

Specimen collection

Five suspected and three probable case-patients presenting to the clinic during 15 – 21 May 2015 provided serum samples to test for mumps-specific immunoglobulin IgM, and buccal swab specimens to test for mumps viral RNA by RT-PCR. The specimens were collected a median of three days (range 1-5) after symptom onset. Buccal specimens were collected using cotton swabs after massaging the parotid gland area for 30 seconds prior to swabbing the area around Stensen's duct. Swabs were then placed in 2 mL of standard viral transport medium (VTM). All samples were maintained at 4°C and were transported on cold packs within 24 hours of collection to TDRC for freezing at -80°C. The samples were shipped on dry ice to the University Teaching Hospital Virology Laboratory in Lusaka for onward shipment to the Measles, Mumps, Rubella and Herpesvirus Laboratory at the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, USA for testing.

Laboratory testing

Serology

Serology testing was performed using a mumps capture IgM enzyme immunoassay (EIA), which was developed and validated at the CDC using a protocol similar to that previously reported for the measles capture IgM EIA [11].

Real-Time reverse transcription PCR

RNA was extracted from buccal swabs using the QIAamp Viral RNA Mini Kit (Qiagen, Cat# 52904). To test for the presence of mumps virus, the RNA was amplified in a one-step RT-PCR assay using the SuperScript® III Platinum® One-Step Quantitative RT-PCR Kit (Invitrogen™, Cat# 11732-088). For each specimen, 2.5 µl of RNA was added to the kit reagents with mumps N-gene specific primers for a total reaction volume of 25 µl. The primers (IDT) used were 5'-GTA TGA CAG CGT ACG ACC AAC CT-3' (MuVN687F), and 5'-GCG ACC TTG CTG CTG GTA TT-3' (MuVN668R), and the probe (IDT) used to detect amplification is 5'-FAM-CCG GGT CTG CTG ATC GGC

GAT-BHQ1-3′. The reactions were incubated at 48°C for 30 minutes, 95°C for 5 minutes, and 40 cycles of 95°C for 15 seconds and 60°C for 1 minute. The RT-PCR was considered positive if there was amplification within 40 cycles.

Genotyping

RNA from patient samples that were positive for mumps virus by RT-PCR was used to amplify a 675 nucleotide fragment of the mumps small hydrophobic (SH) gene. PCR product was obtained using an Invitrogen One-Step RT-PCR kit and cycling parameters of 55°C for 30 minutes, 94°C for 2 minutes, 40 cycles of 94°C for 15 seconds, 55°C for 30 seconds, 72°C for 30 seconds, followed by 72°C for 7 minutes and 4°C hold. The sequence of the PCR product is used to determine the genotype [12]. Primer sequences are SH Forward 5′-AGT AGT GTC GAT GAT CTC AT-3′ and SH Reverse 5′-GCT CAA GCC TTG ATC ATT GA-3′ [13]. The sequencing window is 316 nucleotides and includes the non-coding regions flanking the coding sequence for the SH protein. Sequences from patient samples were then compared to the WHO reference strains to determine genotype [14].

Data analysis

We cleaned data (IDSR line lists) in Microsoft Excel and exported to Epi-Info 3.5.4 for analysis. Continuous variables were summarized using means and medians, while categorical data were summarized using proportions.

Ethical considerations

Investigation of this outbreak was conducted under the public health response authority from MoH's directorate of Disease Surveillance Control and Research and therefore was exempt from formal ethical review. Written informed consent was obtained from all patients who provided specimens.

CDC authorship disclaimer: The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Results

From January through June 2015, a total of 283 mumps cases were reported in Luanshya District. The number of cases reported in April (71, 25% of total) exceeded the number reported in January (57), February (33), March (39), May (56) and June (27) (Figure 1). Cases were primarily clustered in four townships, two of which had the majority of cases: Mikomfwa (48%) and Roan (38%) (Figure 2).

Of 72 case-patients interviewed and examined, 61% were female, and 81% were children aged < 15 years; 29% were aged 1-4 years, and 38% were 5-9 years (Table 1). The median age was seven years (interquartile range 8-54 years).

Clinical characteristics included buccal tenderness (29%), fever > 37.5ºC (29%), and difficulty swallowing (11%). None of the 21 febrile patients tested positive for malaria by RDT. None of the 72 examined case-patients required hospitalization, died, or developed deafness, orchitis, or encephalitis. None reported prior mumps vaccination during the period under review (Table 1).

Mumps was confirmed in seven of the eight case-patients tested: six were sero-positive for anti-mumps IgM antibodies and five had buccal swab specimens that tested positive for mumps by RT-PCR; four of the seven confirmed cases tested positive by both serology and RT-PCR. Genotyping of the PCR-positive cases revealed a common mumps outbreak virus of genotype D (Figure 3).

Discussion

Initiated by review of IDSR data, we identified a laboratory-confirmed mumps outbreak in Luanshya District, Zambia during January through June 2015. This outbreak in an unvaccinated population occurred primarily among school-aged children with no severe complications or deaths. Laboratory confirmation of mumps can be challenging, especially in previously vaccinated or previously infected people therefore, sample collection timing is critical. IgM detection improves when serum is collected three days or more after symptom onset, but RT-PCR detection is most sensitive when specimens are collected within two days of onset. When specimens are taken in this time frame, RT-PCR is more sensitive than serology [4]. Furthermore, only molecular testing allows for genotype determination, which is the only way to distinguish vaccine reaction (i.e., infection related to the live vaccine virus) from a wild-type infection. Genotype D was identified in the tested patients. This genotype was first described in 1969 in Croatia and has only been sporadically detected since that time [9]. Since 2005, in the WHO Americas region (AMRO), the United States has only reported two occurrences of D genotype (2009, 2012) (McNall *et al*, unpublished), and Canada has detected four (2007, 2008, 2009, 2011) with two cases being imports from the WHO African region (AFRO) [15]. Genotype D was detected in a mumps case in South Africa in 2009 [15]. Routine mumps surveillance (and therefore genotyping) is not as robust as measles and rubella surveillance, so the global distribution of mumps genotypes is not well described.

Over three quarters of all mump cases in this outbreak occurred in school-aged children. In an unvaccinated population, this age group is more susceptible to mumps when compared to infants who are protected by maternal antibodies up to age ~9-12 months [4]. According to a media report [6], a 2012 mumps outbreak in Marashda, Egypt showed similar epidemiology with 60% of 100 cases being aged 1-14 years. School absenteeism reportedly increased to 70% during the outbreak, with reports that children did not attend school due to fear of infection. Although we did not have access to baseline school absenteeism data in the district, one primary school did report 13% absenteeism among students in grades 1-4 during the outbreak period, February – April 2015 (data not shown). None of the confirmed mumps cases in this outbreak had been vaccinated, which was expected given that mumps vaccination is not included in Zambia's EPI. Studies from three outbreaks suggest that with 1 dose of mumps vaccine, the effectiveness ranged from 73% to 91% while 2 doses range from 91% to 95% [16]. A study in United Kingdom indicated that nearly 70% of notified mumps cases during 2004 occurred in unvaccinated individuals who had not been targeted by the national vaccination program [16,17]. Immunization coverage of 70-80% among children has been reported to reduce mumps cases by 97% in a population [5].

WHO has recommended routine mumps vaccination in countries with a well-established, effective childhood vaccination programme and the capacity to maintain high levels of vaccination coverage (> 80%) with routine measles and rubella vaccination and where the reduction of mumps incidence is a public health priority [9]. In terms of mortality and disease burden, WHO considers measles control and the prevention of congenital rubella syndrome to be higher priorities than the control of mumps. However, for countries

that decide to use mumps vaccine, the combination of mumps vaccine with measles and rubella vaccines is recommended [9]. Mumps vaccination programs have facilitated dramatic decreases in mumps incidence and even elimination in several countries worldwide [2, 5]. Studies document persistence of antibody in a large proportion of vaccinated populations, and a global review on mumps vaccine literature showed that 73% of children who received MMR vaccine at 18 months of age remained seropositive 10.5 years later [2, 18]. Despite the increase in coverage of diphtheria, tetanus, pertussis, hepatitis B, polio, *Haemophilus influenza* type B (DTP-HepB-Hib 3) and measles vaccination in Zambia since 1992, mumps vaccine has not been available. Mumps is a vaccine preventable disease, and so measures designed for mumps control should aim to prevent it completely through vaccination. In the case of measles, for example, the observed decline in annual measles incidence was 98.7 to 2.4 per 10,000 persons between 2001-2008 in Zambia: a decline attributed to intensive vaccination campaigns [19]. In September 2016, the Government of the Republic of Zambia introduced a combined measles rubella vaccine, spending about $4.3 million to vaccinate approximately seven million children between the ages nine months to 15 years [20]. Besides the newly introduced rubella vaccine, Zambia with its cooperating partners such as WHO, United Nations International Children Emergency Fund (UNICEF), has for a long time conducted mass vaccination campaigns. So far Zambia has met WHO's criteria for introducing mumps vaccine having attained national immunization coverage of > 80%. Between 2001 and 2008, measles vaccine coverage ranged between 84% - 85% [19]. If Zambia considered adding the mumps antigen to EPI, consistently high vaccination coverage would minimize the risk of frequent outbreaks in the setting of high numbers of unprotected older age groups, who are at higher risk of complications of mumps infection.

Zambia's EPI includes a second dose measles vaccination adopted as a "two opportunity" measles strategy aimed at improving vaccination coverage and simultaneously at achieving and maintaining high population immunity against measles. Therefore, the platform for two doses of mumps vaccination would already be in place. Data on the burden and epidemiology of mumps remain limited, which prevents the ability to conduct a cost-benefit analysis of vaccination. Additional data, including data from non-outbreak settings, are needed to inform decision making about mumps vaccination. In the meantime, mumps outbreaks are likely to continue in Zambia. No complications were identified among reported mumps cases in this outbreak. While mumps is not often fatal, serious complications can occur. Previous outbreaks have documented complications such as encephalitis, which can result in death or disability [5], and mumps in adolescent males can cause orchitis [2, 5]. Mumps virus can also affect the pancreas or, in females, the ovaries [5]. In our investigation, clinical information was only available for the cases identified through active case-finding in just one district, thereby limiting inferences about the frequency of complications and death. Zambia has a high prevalence of HIV(13.4%) [21], which might increase the risk of complicated infections. Assessing outcomes and complications of mumps in Zambia using data from a large sample is needed for a complete epidemiologic description.

The absence of reported mumps cases or outbreaks in other provinces of Zambia might be related to a low level of disease awareness in facilities, because mumps is not a notifiable disease in IDSR. It is likely that mumps outbreaks have occurred in Zambia but have not been recognized or reported. Further, routine laboratory testing for mumps in Zambia is not available. There is need for locally available laboratory testing for mumps, at least at national level; this will significantly improve mumps surveillance in the country. Our findings have additional limitations. Our investigation captured only passively reported through IDSR prior to May 2015. Data from an outbreak may not represent the typical epidemiology of disease. Therefore, data from cases identified through surveillance over a longer period would be needed to better understand the epidemiology and clinical characteristics. Additionally, data from one district might not be representative of the whole country, although our findings are consistent with descriptions of mumps in other regions of the world.

Conclusion

Our findings represent the first reported epidemiologic description of mumps in Zambia, and the second report of mumps genotype D in Africa. While the epidemiology is consistent with prior descriptions of mumps in unimmunized populations, and no serious complications were identified, these data should inform policy discussions regarding mumps vaccination in Zambia. There is need for further work on mumps epidemiology and burden in Zambia to determine the magnitude of the problem.

What is known about this topic

- Mumps is a vaccine preventable viral disease which may cause deafness, orchitis, encephalitis or death;
- Outbreaks occur regularly in unvaccinated populations and most commonly affect young, school-aged children;
- Although mumps is not a notifiable disease in Zambia, cases are sometimes reported through the Integrated Disease Surveillance and Response (IDSR) system.

What this study adds

- First reported epidemiologic description of mumps in Zambia, and second report of circulating mumps genotypes in Africa;
- Routine mumps surveillance (and therefore genotyping) is not as robust as measles or rubella surveillance;
- Mumps outbreaks are likely to continue in Zambia and there is a need for additional data for informed decision-making about mumps vaccination.

Competing interests

The authors declare no competing interests.

Authors' contributions

Ernest Kateule, Victor Daka and Webster Kasongo conceived of the investigation, participated in its design and coordination, drafted the manuscript, initiated the investigation, interpreted the results and drafted the final manuscript. Kelvin Banda was involved in data collection. Raydel Anderson, Rebecca McNall and Marcia McGrew conducted laboratory testing, interpreted and analysed the findings. Ramya Kumar, Modest Mulenga and Kip H. Baggett revised the methods and guided the discussion and write up of the manuscript. All authors read and approved the final manuscript.

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Table and figures

Table 1: Demographic and clinical characteristics of patients with mumps, Luanshya District, Zambia, May – June 2015 (n = 72)
Figure 1: Mumps cases by date of onset of illness in Luanshya District, Zambia, December 2014 – June 2015 (n = 283)
Figure 2: Mumps cases by township in Luanshya District, Zambia, January – June 2015
Figure 3: Genotyping results of mumps outbreak virus (genotype D) and their relationship to other described mumps genotypes in the world - June, 2015

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Table 1: Demographic and clinical characteristics of patients with mumps, Luanshya District, Zambia, May – June 2015	
Characteristic	**Number (%)**
Gender (Female)	44 (61)
Age Group (years)	
<1	0 (0)
1-4	21 (29)
5-9	27 (38)
10-14	10 (14)
15-20	7 (10)
>20	7 (10)
Residential Areas	
Mikomfwa	41 (59)
Roan	18 (25)
Signs & Symptoms	
Swollen parotid/other salivary glands	72 (100)
Tenderness of buccal area	21 (29)
*Fever (Temp. > 37.5°C)	21 (29)
Difficulty swallowing	8 (11)
Outcome	
Hospitalised	0 (0)
Deaths	0 (0)
Vaccinated for mumps	0 (0)
*All temperatures were determined axillary	

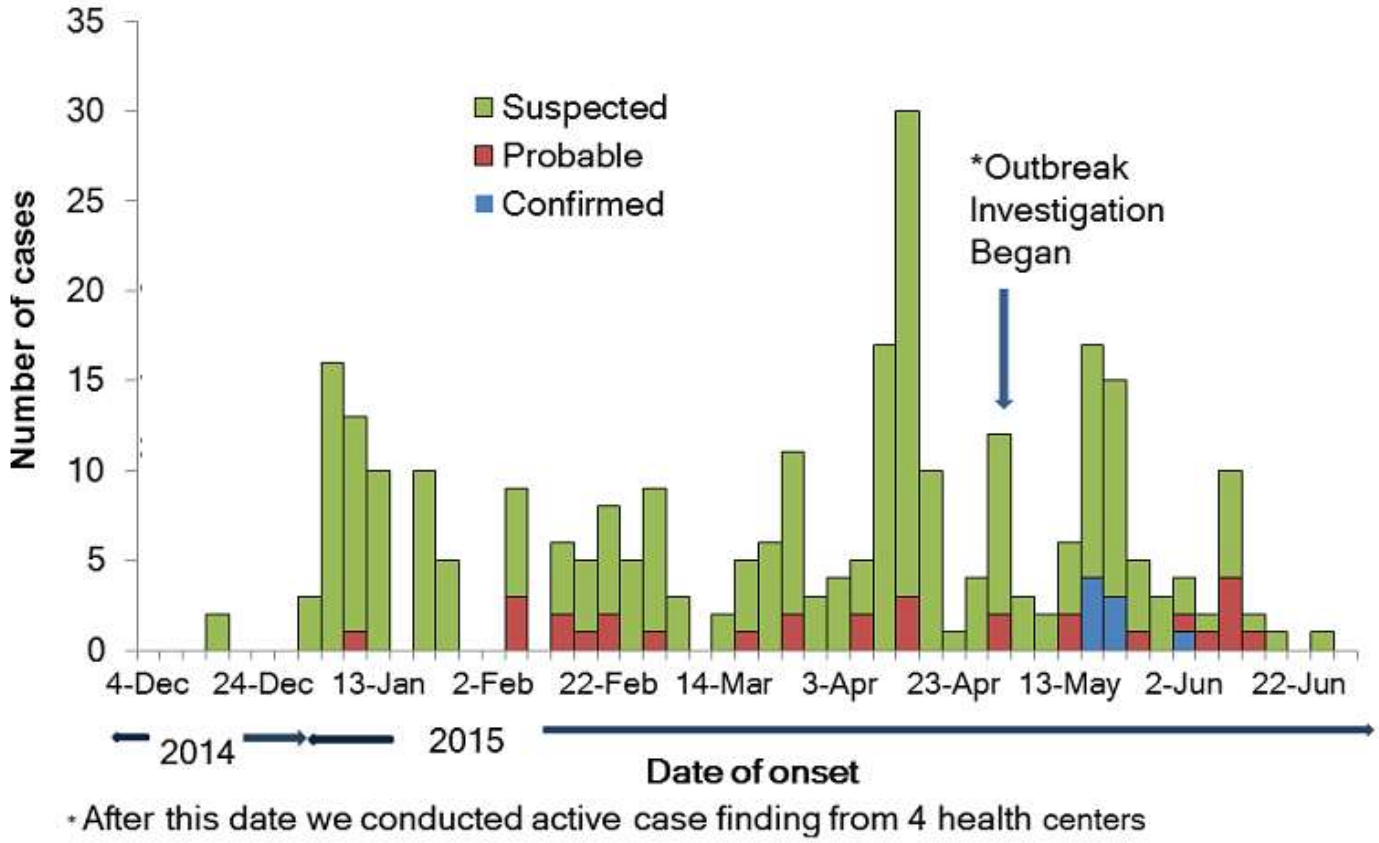


Figure 1: Mumps cases by date of onset of illness in Luanshya District, Zambia, December 2014 – June 2015 (n = 283)

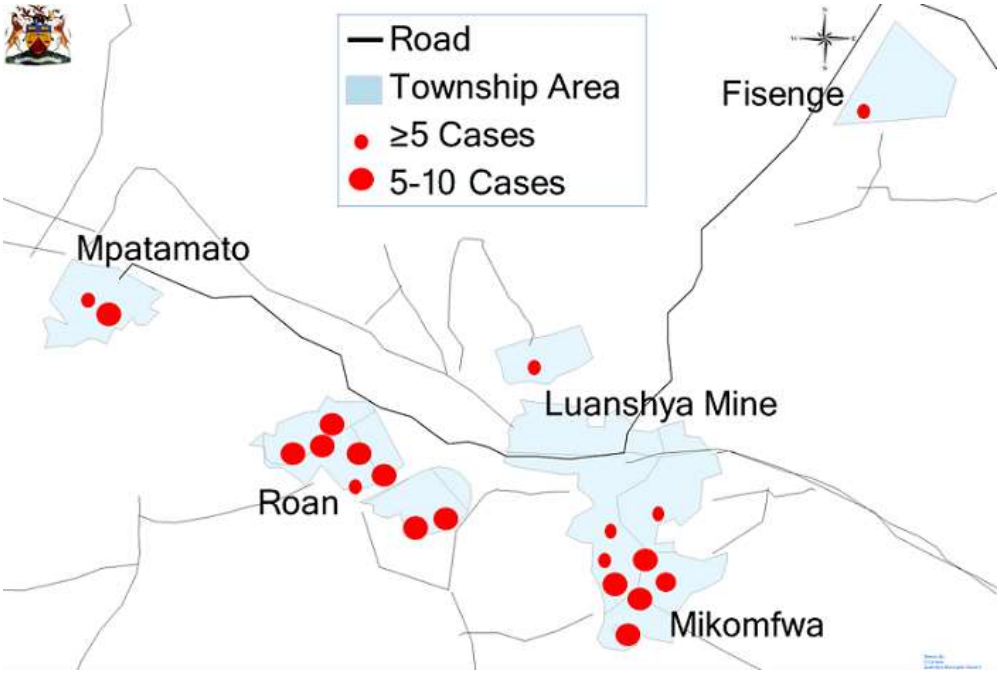
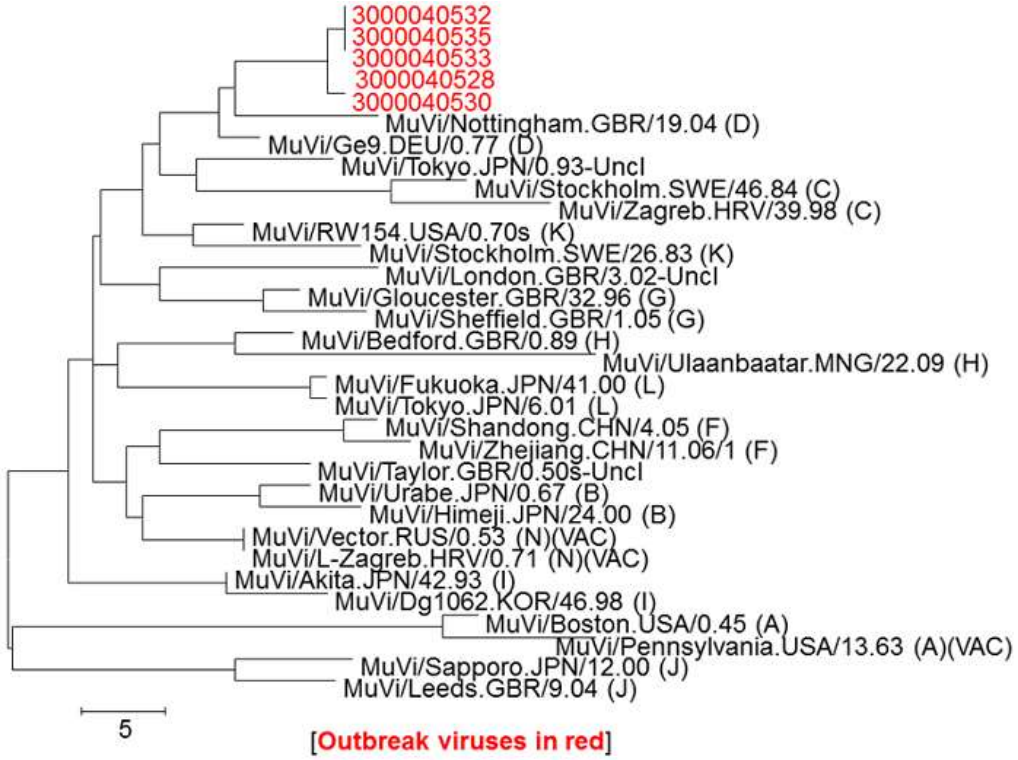


Figure 2: Mumps cases by township in Luanshya District, Zambia, January – June 2015



Maximum Parsimony analysis of taxa. The percentage of replicate trees in which the associated taxa clustered together in the bootstrap test (500 replicates) are shown next to the branches. Evolutionary analyses were conducted in MEGA.

Figure 3: Genotyping results of mumps outbreak virus (genotype D) and their relationship to other described mumps genotypes in the world - June, 2015