



Nosocomial outbreak of measles amongst a highly vaccinated population in an English hospital setting

L. Berry^{a,*}, T. Palmer^b, F. Wells^c, E. Williams^d, B. Sibal^b, J. Timms^e

^a *University Hospital Coventry and Warwickshire NHS Trust Coventry, United Kingdom*

^b *Communicable Disease Control, West Midlands Health Protection Team, Public Health England, Birmingham, United Kingdom*

^c *Infection prevention and control, University Hospital Coventry and Warwickshire NHS Trust, United Kingdom*

^d *Coventry & Warwickshire Occupational Health Shared Service, University Hospitals Coventry and Warwickshire NHS Trust, United Kingdom*

^e *Department of Virology and Molecular Pathology, Coventry and Warwickshire Pathology Services, University Hospital Coventry and Warwickshire NHS Trust, United Kingdom*

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SUMMARY

In May 2017 a patient attended the emergency department at a hospital in England, with a presumed allergic reaction. He was subsequently diagnosed with measles. There were seven further confirmed cases, five of whom had received two doses of MMR vaccine. This outbreak highlights the importance of not relying on vaccination status to rule out the diagnosis of measles. Epidemiological investigations of this outbreak were particularly challenging due to the highly infectious nature of the measles virus, and prevented full elucidation of either the source of this outbreak or the transmission pathways.

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Introduction

Prior to the introduction of the vaccine in 1963, measles was a leading cause of childhood mortality and morbidity, responsible for over 2 million deaths worldwide per annum. Introduction of measles containing vaccines has resulted in a

significant decrease in the number of infections. A reduction in vaccine uptake globally has allowed measles cases to increase significantly [1]. In the UK and Europe pockets of transmission have occurred, there were 13,475 cases reported across the EU/EEA between May 2017 and April 2018 [2].

Following delays in diagnosis of a case of measles admitted to a large tertiary referral teaching hospital, an outbreak of 7 further confirmed cases occurred, amongst both hospital staff and the community. Unusually, the majority of the subsequent cases were fully vaccinated.

* Corresponding author. Lisa Berry, University Hospital Coventry and Warwickshire NHS trust Coventry, United Kingdom.

E-mail address: Lisa.berry@uhcw.nhs.uk (L. Berry).

Outbreak description

Hospital cases

In May 2017 a 25 year old male patient attended the Emergency Department (ED) at an English teaching hospital. He presented with a 1 day history of a rash on his face with accompanying facial pain, diarrhoea and epigastric tenderness. He was found to be lymphopenic. He had visited his primary care physician the day before feeling generally unwell and with a facial rash. The rash was first noticed after he had taken 'Night Nurse', [a proprietary medicine containing paracetamol, promethazine hydrochloride, and dextromethorphan hydrobromide], for symptom relief the day before. A presumed allergic reaction was diagnosed, for which he was prescribed prednisolone. Following the ED attendance he was discharged home, and advised to continue the prednisolone.

On the following day he re-presented to the ED via ambulance with a temperature of 40°C and conjunctivitis; the rash had now spread to his torso and limbs and he was coughing up sputum. He was admitted to the Acute Medical Unit (AMU). He continued to deteriorate and 48 hours later was transferred to the Intensive Care Unit (ICU) with type 1 respiratory failure and was ventilated using continuous positive airway pressure (CPAP). On review a clinical diagnosis of measles pneumonitis was made, which was later confirmed in the local laboratory by PCR on an oral fluid swab. He had received one dose of MMR as a child (no exact date available), but had experienced a reaction to the vaccine and therefore did not have his second dose. Infection control measures were implemented on clinical diagnosis. This comprised of being nursed in a negative pressure side room on ICU and healthcare workers wearing airborne droplet PPE; gowns, aprons, gloves, surgical mask and visor.

On transfer back to the ward, the room was left vacant for two hours to allow for droplets to settle prior to cleaning, and cleaners to clean the room wearing PPE. This is local standard practice for cleaning when patients with measles are transferred or discharged. The local health protection team were informed of the diagnosis, and contact tracing commenced. Three hundred and eighteen contacts were identified in the hospital and 85 in the community, including household contacts. Due to delays in the initial diagnosis, no prophylactic interventions were offered to those who would have received them if the diagnosis had been made earlier. Despite robust epidemiological investigations, the source of measles in the index case could not be identified. He reported no travel and to his knowledge was not in contact with a known case of measles. Genotyping of samples revealed that the virus was genotype B3 which is widely circulating in Europe including a large Romanian outbreak. The index case was known to work in a workplace that employed a number of Romanian nationals and therefore it was hypothesised that this may have been the source of infection.

Eleven days after the first presentation to ED of the index case, a 38 year old female presented to ED with pyrexia, myalgia and lower back pain. A urine dipstick suggested a diagnosis of urinary tract infection so she was discharged home on antibiotics. Forty-eight hours later she represented with worsening fever, rash, diarrhoea, hoarse voice and a red pharynx. On examination, spots were noticed on the back of

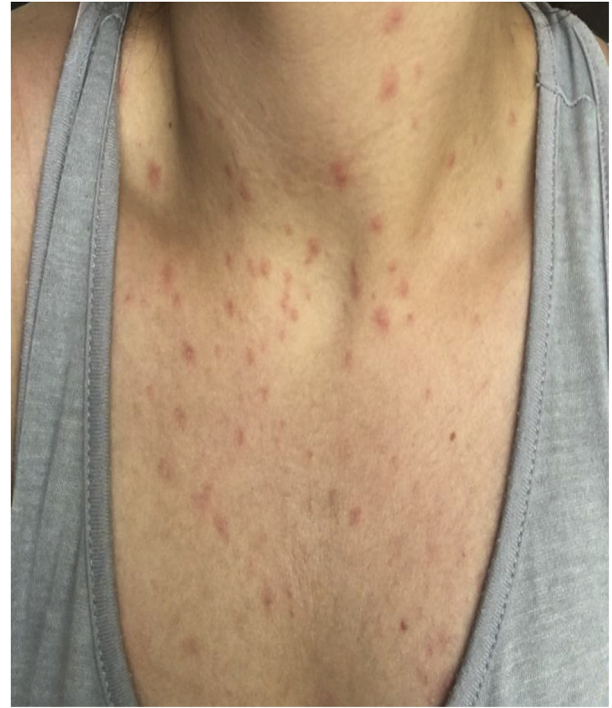


Figure 1. Photograph showing the attenuated measles rash from hospital case 4. Consent given for photograph to be used.

her throat and her full blood count showed lymphopenia. She was clinically diagnosed with measles which was confirmed locally by PCR on an oral fluid swab. She was isolated on clinical diagnosis but had not been isolated prior to that. Her clinical picture progressed and she developed hepatitis. She had not received any measles-containing vaccine, so was non-immune to measles. This case was a healthcare worker (HCW) at the hospital and had worked in the ED on the day when the index case first presented, although no defined contact was identified. Five hundred and sixty six contacts were identified, the majority of whom were deemed to be immune to measles due to natural infection i.e. born before 1970 [3]. However, 2 patients were advised to be given IV HNIG due to their immunosuppressed status. In addition there were 88 community contacts.

Between 13 and 17 days after the index case presented to ED, four further cases were diagnosed in hospital healthcare workers. Three HCWs presented with general malaise, an attenuated rash (Figure 1) and lymphopenia. Measles would not have been suspected had it not been for the epidemiological link. All cases had oral fluid swabs obtained and all were RNA positive. Genotype B3 was identified in all swabs where genotyping was possible. All except one of these cases had a vaccination history (Table I). One HCW had no vaccination record but had an employment serology result that was IgG indeterminate but declined a vaccine booster. The one case that presented with a typical measles rash and was unwell enough to be admitted to hospital had a history of two doses of MMR but there was a ten year gap between doses. The timeline of all the hospital acquired cases in relation to the index case is shown in Figure 2.

Table 1
Summary of laboratory findings and vaccine status of the cases. Serology results are all on serum samples unless stated. *OF = Oral Fluid

Case	MMR status	Clinical course	RNA results and genotyping where appropriate (oral fluid sample)	Cycle threshold (Ct)	Serology results (sample type)		
					IgM Serum	IgG Serum	IgM Oral Fluid / IgG Oral fluid
Index	1 dose	Hospitalised including ITU admission	RNA detected Genotype B3	24.0	Positive	Positive	Negative
Community case 1 (Partner)	2 doses	Mild attenuated	RNA detected	38.05	Not tested	Not tested	Positive
Community case 2 (paramedic)	2 doses	Mild attenuated	RNA detected	28.4	Equivocal	Positive	Negative
Hospital worker Case 1	None	Hospitalised	RNA Detected	23.3	Negative	Negative	Negative
Hospital worker Case 2	2 doses	Mild attenuated	RNA Detected	30.2	Negative	Positive	Positive
Hospital worker Case 3	2 doses (10 years apart)	Hospitalised	RNA Detected	30.5	Negative	Positive	Negative
Hospital worker Case 4	2 doses	Mild attenuated	RNA Detected	30.5	Positive	Positive	Positive
Hospital worker Case 5	No MMR on record. (IgG indeterminate employment screen)	Mild attenuated	Genotype B3 RNA Detected Genotype B3	31.0	Negative	Positive	Negative Positive

Community cases

There were 2 laboratory confirmed cases of measles and one case that was a likely case of measles (as defined by Public Health England definitions [4]) linked to this outbreak. The first laboratory confirmed case of measles was the partner of the index case. This case was tested by the national reference laboratory using an oral fluid testing kit. She had received two doses of MMR. The other laboratory confirmed case was a paramedic who transported the index case to hospital on the second admission. A summary of all the laboratory results and MMR status of the cases can be seen in Table 1. The likely case was a 14 month old child who lived with the index case and who had not yet received their first dose of MMR vaccine. This child presented to the children's ED having developed a rash and fever in a timeframe that was consistent with a transmission event, but all laboratory tests for measles were negative both at the hospital and at the reference laboratory.

There were no further cases reported and the outbreak was considered closed twenty one days after the rash onset of the last case.

Discussion

This outbreak occurred in a highly vaccinated population, with the majority of secondary cases (5/7 or 71.4%) having had the MMR vaccine. Given the considerable efficacy of the MMR vaccine, this is unusual. Of the cases with documented vaccination, four presented with an attenuated infection, with mild symptoms and may not have been diagnosed in the absence of the contact history, the considerable publicity within the hospital (3 cases) or follow up of community contacts (1 case). None of these cases resulted in further transmissions. These were considered to be re-infections [4]. Re-infections are usually mild, with attenuated rash, reduced viral shedding and reduced risk of onward transmission, as was highlighted in this outbreak. In a healthcare setting, however, we would advise that follow up of contacts of these re-infection cases is necessary. The reason for this is twofold; firstly in an outbreak setting you won't have time to formally differentiate between re-infection and vaccine failure if you have a patient or member of staff with a rash, epidemiological link and positive laboratory results, you need to follow up contacts. Secondly, from Table 1 it can be seen that there is still RNA in the oral fluid at a sufficient level that viral shedding still occurs, albeit at significantly lower levels, which when the case is a member of hospital staff may result in transmissions to highly vulnerable patients. This outbreak illustrates that vaccination history should not be used to rule out clinical cases of measles when a patient presents with rash and fever.

The delay in diagnosis in this outbreak and subsequent delay in implementation of infection control measures in the first two cases resulted in significant contact tracing and further cases. Fortunately, none of these were unvaccinated individuals. This was potentially due to the layout of the hospital; the index case would have been in an adult ED, the children's ED is in a different area, therefore the majority of contacts were older and either vaccinated or had natural immunity.

It is unclear why the majority of re-infection cases arose in the hospital setting, rather than in the community. A clear contact was only identified in three of the re-infection cases;

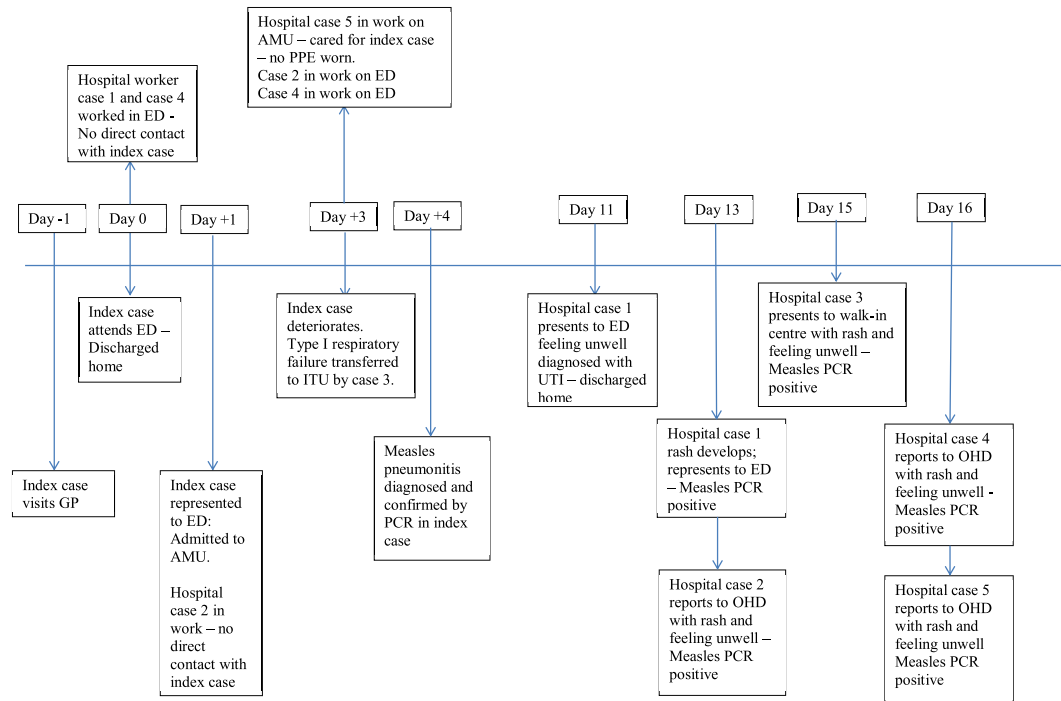


Figure 2. Timeline of hospital acquired measles cases.

two from the community and one healthcare worker. The other three re-infection cases had no known direct contact with the index case, although they were present in the ED at the same time. Measles is a highly contagious infection and it is well recognised that the virus can remain present in the environment. We suggest that transmission in these three cases was either due to a fleeting contact in the corridor or recirculation of air. It is possible the initial steroid treatment for a presumed allergic reaction increased the amount of virus being shed in this individual.

Vaccination of the HCWs in this outbreak did not prevent infection but did result in attenuated infections with no secondary transmissions. HCW contact tracing identified 132 HCWs that had been in contact with a case. Investigations undertaken by the local occupational health team identified that vaccination records were not available for all HCWs. Seven HCWs who were contacts, were found to be IgG negative, they were advised to stay off work and offered vaccination. This outbreak highlights the importance of keeping HCW vaccination records up to date, although this is a difficult task as there is a reliance on HCW to respond to recall letters, when data is missing or are noted to be non-immune. HCWs in the UK have a recognised duty to protect themselves, their colleagues and their patients. This includes minimising risk of communicable diseases, as covered in the Health and Safety at Work Act (1974). However, vaccination is not currently mandatory for HCWs and some will fail to produce antibodies even after being vaccinated. This makes implementing and enforcing robust occupational health standards around vaccination or antibody status challenging. This can be further complicated by the extensive use of locum and bank HCWs, although this was not a factor in this outbreak.

Recent decreases in the numbers of vaccinated individuals in the UK and Europe has allowed for pockets of transmission to

occur with outbreaks being reported in countries across the continent [2,5,6]. There is substantial evidence that antibody levels against measles do wane over time. What this combination of reduced vaccine uptake, waning antibody and lack of immune boosting via exposure to wild-type virus means in practice and what the implications will be for occupational health recommendations is unclear [7,8].

In a study by Fiebelkorn et al [9] a third dose of MMR in a cohort of 662 individuals was investigated. The study did not support universal use of a third dose of MMR, as individuals who were seropositive, did not have a response to this extra dose of vaccine. However, in individuals with a low pre-booster antibody level, there was an increase in the antibody level. This may support a change in approach to occupational health screening for measles immunity where staff members will require a pre-employment antibody level test; giving a booster dose to those with waning levels. However, this approach requires further investigation. If population vaccine coverage is maintained at levels greater than 95%, i.e. the level required [10] to prevent measles circulating, this may not be necessary. However, in areas where vaccination levels have dropped, such as in the UK, this may need to be considered to avoid outbreaks similar to this one, and help control further cases by reducing secondary transmission.

As vaccination rates decline the role of waning antibody may result in an increase in re-infections when wild-type virus is sporadically re-introduced. This may result in more outbreaks such as the one described here.

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