



## Short communication

# Mumps outbreak and MMR IgG surveillance as a predictor for immunity in military trainees



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## ABSTRACT

In 2017, a mumps outbreak occurred in a barrack holding 249 service members. Suspected cases were evaluated with a combination of mumps IgG, IgM, viral culture, PCR and sequencing. Seven cases were diagnosed in febrile patients presenting with parotitis or orchitis. Mumps infection was confirmed by IgM or positive PCR with 5/7 cases having notable IgG levels before infection. Sequencing confirmed mumps genotype G strain. Serum from all 249 service members collected prior to the outbreak was withdrawn from the Department of Defense (DoD) Serum Repository and the IgG values of measles, mumps and rubella determined with 20.2%, 12.3% and 9.7% service members being seronegative, respectively. No specific IgG seronegativity combination predicted IgG marker levels to another virus within the same vaccine. This paper provides additional evidence that mumps serology is not a reliable surrogate for mumps immunity and that we need better laboratory correlates to confirm immunity.

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## 1. Introduction

Mumps is a viral infection clinically characterized by parotitis, orchitis or oophoritis. Per Center for Disease Control (CDC), a probable case is defined as acute salivary gland swelling, orchitis, or oophoritis in a person with a positive serum anti-mumps IgM or with an epidemiologic link to another probable or confirmed case [1]. A confirmed case is any person with a positive mumps RT-PCR or culture with an acute illness compatible with mumps. The majority of cases are clinically evident; however, approximately 20% of those infected remain subclinical or asymptomatic, leading to various carrier states that may prolong outbreak events [2]. Sequelae of mumps infections includes decreased testosterone production, oligospermia, transient hyperglycemia, and rare sensorineural deafness [3]. Similar to other respiratory viral illnesses, mumps is easily transmitted in settings with close proximity, such as schools and military barrack settings. Furthermore, we assume immunity based on laboratory detection and semi-quantification of mumps IgG titers in serum. Mumps outbreaks are increasing at an alarming rate with several factors and theories suggested

including the diversification of viral strains and the evolutionally pressures to subvert control and eradication efforts [4,5]. This raises the question if current vaccines need to be reformulated to capture circulating viral strains, especially those implicated in outbreaks.

In 2017, a mumps outbreak occurred within a military company. A team of providers, laboratorians, and public health assembled to identify cases, contacts, and predict the infection or immunity status for all service members within the company. Prompt identification and response limited the outbreak. Mumps IgG titers were measured on pre-outbreak serum samples withdrawn from the Department of Defense serum repository for all the potentially exposed and infected service members within the company. The assumption of immunity based on childhood vaccine documentation and laboratory testing are discussed, which may be relevant factors in interfering mumps protection despite the reemergence of this infectious disease.

## 2. Cases

On April 13, 2017, five trainees (Patients A-E) from the same company undergoing Army Individual Training (AIT) were admitted for mumps evaluation (Table 1). Patient A presented to a military trainee health clinic on April 11 for facial swelling. On April 13, patients B-E were seen for parotid swelling, leading to referral of

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**Table 1**  
Demographic and laboratory results for patients A–K during April–May 2017 mumps outbreak in Texas.

Patient	Age	Accession IgG Serology <sup>a</sup>		Symptom Onset	Diagnosis	Mumps Serology at Evaluation <sup>b</sup>		Viral Culture	Mumps RT-PCR	Case Definition <sup>c</sup>
		Measles	Rubella			IgG	IgM			
A	19	+	+	7-Apr	Soft Tissue Edema	8.3	<0.8	–	–	P
B	20	+	+	8-Apr	Mumps, Parotitis	8.2	1.11	–	–	P
C	20	+	+	10-Apr	Mumps, Parotitis	6.6	3.02	+	+	C
D	23	+	+	11-Apr	Mumps, Parotitis	7.2	<0.8	–	+	C
E	26	+	+	11-Apr	Mumps, Parotitis	5.5	<0.8	+	+	C
F	19	+	+	21-Apr	Enterovirus/Rhinovirus	7.3	<0.8	–	–	R
G	20	+	+	23-Apr	Mumps, Submandibulitis	3.3	<0.8	–	+	C
H	19	+	+	24-Apr	Viral Syndrome	3.4	<0.8	–	–	R
I	20	+	+	25-Apr	<i>C. pneumoniae</i>	4.1	<0.8	–	–	R
J	23	+	+	1-May	Mumps, Epididymo-orchitis	7.7	<0.8	–	+	C
K	25	–	+	4-May	Enterovirus/Rhinovirus	1.1	<0.8	–	–	R

<sup>a</sup> Serologies conducted at time of entrance into military service, –, non-immune status, +, positive immune status.

<sup>b</sup> Serology at hospital presentation, antibody index values  $\geq 1.1$  are considered significantly higher than non-exposure, non-vaccinated populations.

<sup>c</sup> R, rejected; P, probable; C, confirmed according to CDC Mumps case definitions, 2012.

patients A–E to a military hospital where they were subsequently admitted and placed under droplet precautions. Army Public Health Nursing (APHN) started contact investigations and implemented enhanced surveillance. Nasopharyngeal swabs were collected from suspect mumps patients and the Biofire respiratory pathogen panel (RPP) performed to rule out non-mumps etiologies. Nasopharyngeal swabs for RPP testing and serum testing for mumps IgG/IgM ELISA (BioRad, Hercules, CA) were performed in-house while buccal swabs for mumps RT-PCR and viral culture were sent to a reference facility (ARUP Laboratories, Salt Lake City, UT) at the time of presentation. Mumps virus detected by RT-PCR or viral culture was further sequenced for epidemiological relatedness. Patients C–E were diagnosed with confirmed mumps, whereas patient A and B were diagnosed with probable mumps based on symptoms and either having an epidemiological linkage to other confirmed mumps cases or elevated IgM antibodies, respectively.

All trainees provided documentation of two childhood doses of measles-mumps-rubella (MMR) vaccine or demonstrated positive serology for both measles and rubella prior to military service. Mumps serology testing is not required upon accessioning and immune status to mumps was inferred by positive serology to measles and rubella in accordance with Army policy. Trainees live in barracks, a congregate living facility. At the time of this outbreak, the CDC suggested administration of a third mumps containing vaccine in the following circumstances: high two-dose vaccination coverage, intense exposure setting, and a high attack rate [6]. As all of these criteria were met, a third MMR vaccine was administered to the entire trainee population (420 soldiers).

After administration of a third MMR vaccine, enhanced surveillance identified additional trainees that required mumps evaluation. An evaluation algorithm was established to screen trainees from the affected company with complaints of similar signs and symptoms consistent with mumps. After the evaluation algorithm was implemented, patients F through I were admitted on April 26. Patient F had symptoms consistent with upper respiratory tract infections and G presented with submandibular swelling. Patient G was confirmed to have mumps with a positive mumps RT-PCR while F was rejected as a mumps case due to positive RPP for Rhinovirus/Enterovirus (Table 1). Patients H and I did not meet mumps diagnostic criteria. Patient H was diagnosed and discharged with *C. pneumoniae* and patient I discharged with non-mumps viral symptoms based on a combination of the BioFire respiratory panel and serology with no further clinical evidence of mumps infection. As an additional precaution, the isolation beds were created in the barracks for discharged patients requiring

ongoing precautions or those that did not require inpatient evaluation, consistent with published guidelines [7].

A week later, two additional trainees were evaluated for mumps, with patient J presented on May 2, 2017, with epididymo-orchitis and had a positive buccal RT-PCR, confirming a mumps diagnosis. Patient K presented with facial swelling but mumps was not confirmed since all mumps-specific tests were negative and the RPP detected rhino/enterovirus nucleic acid. In total, there were five confirmed cases and two probable cases of mumps from April 13–May 4, 2017.

Through contact tracing, Public Health retrospectively identified patient zero (Z) as a potential first case of mumps in the local outbreak. Patient Z presented to the hospital and was admitted with bilateral mandibular and parotid gland swelling on February 25 after transfer to AIT following basic military training (BMT) in another state. On March 1 his mumps IgM was reported as indeterminate (0.96 antibody index (AI), indeterminate range 0.8–1.2 AI) and a RPP was PCR positive for Rhinovirus/Enterovirus. The patient was released after swelling was resolved without further testing. Patient Z was recalled in late April and convalesce serum samples were positive for mumps IgM levels at 3.3 AI. Upon record review, Patient Z was housed in close quarters with another service member who had been diagnosed with pharyngitis on January 20, 2017 during BMT for complaints of left sided facial and neck swelling. No mumps testing was done at the BMT site. It is likely that patient Z served as the local outbreak index case after transition from BMT to AIT, importing the mumps virus to Texas. It is probable there were additional unrecognized cases during January–April 2017, as mumps incubation lasts up to 25 days and the infectious period lasts up to 14 days causing asymptomatic or subacute infections that does not necessitate medical evaluation.

### 3. MMR immunity surveillance and outcomes

To access the robustness of screening servicemembers for mumps immunity, as inferred by IgG AI values  $\geq 1.1$  per manufacturer's guidelines, and gauge the potential effectiveness of administering an additional vaccine dose, sera were requested for trainees in the first company affected by mumps during April 2017. This was given a non-research determination by the local IRB committee. Sera were requested from the DoD Serum Repository Center which archives serums drawn upon military accession and thereafter. Two hundred and ninety-nine serum samples were received from 249 individuals (age range 20–38, median 24.7 years, 234 male and 79 female). MMR IgG AI values were measured using the Bio-Rad ELISA (Hercules, CA) assay to determine

the sero-positivity to measles, mumps, and rubella was adequate across the group of service members in the company prior to administration of the third MMR vaccination or onset of disease. There were 38 individuals who had two or more serum samples banked in the repository with each sample collected at least one year apart from one another. The average change in IgG AI value between the first serum deposited into the repository and the most recent for 36 of the 38 paired sera sets was  $0.08 \pm 0.04$  SD with a mean temporal separation of 3.66 years (min = 72 days, max = 10.6 years), suggesting IgG levels remained consistent. The longest duration between any two samples spanned June 2003 to December 2013 with IgG values of 5.45 and 5.36, respectively. In the two individuals with a relatively large change in paired sera IgG levels, one had a decrease from 1.08 to 0.55 AI between July 2011 and October 2016 and the other individual's antibody levels decreased from 3.58 to 1.71 between January 2015 and November 2016.

Two of the seven patients diagnosed with probable or confirmed mumps infection had mumps IgG index values below the immunological cut-off value for protective immunity (Table 2). The remaining five had sufficient IgG antibodies ranging from an index of 1.16–4.53. Serologies obtained in acute and convalescent phase showed markedly higher IgG values than pre-mumps infection. Patients B and C had elevated IgM acute phase values whereas all other patients did not. No increase in mumps IgM values was noted in convalescent samples of infected patients.

Mumps IgG levels were evaluated in all of the service members within the same barracks to determine if current screening practices are sufficient predictors of mumps immunity (Table 3). Eighty-four of 299 were seronegative to at least one component of the MMR vaccine with 2.7% being below predicated immunity levels to all three viruses. Sixty of the 299 pre-outbreak sera had IgG concentrations below the AI value considered protective for mumps (Fig. 1).

**Table 2**  
Mumps serologies of infected patients.

Patient	Date Serum Collected	Sample ID	Mump IgG index value <sup>a</sup>	Mump IgM index value
A	09/28/2016 04/11/2017	S535148751	1.16	
		Acute	8.3	<0.8
		Convalescent	7.1	0.8
B	5/31/2016 10/05/2016 04/11/2017	S328846581	2.06	
		S419574062	2.63	
		Acute	8.2	1.11
Convalescent	7.3	ND <sup>b</sup>		
C	07/07/2016 04/11/2017	S871575977	<b>0.6<sup>c</sup></b>	
		Acute	6.6	3.02
		Convalescent	8	3.3
D	03/26/2012 09/14/2016 11/22/2016 04/11/2017	S159423436	2.5	
		S280327263	2.18	
		S289662433	3.21	
		Acute	7.2	<0.8
Convalescent	7.4	0.8		
E	07/29/2016 11/23/2016 04/11/2017	S986141489	1.29	
		S394245693	1.4	
		Acute	5.5	<0.8
Convalescent	7.2	0.8		
G	08/10/2016 11/22/2016 04/24/2017	S483180970	<b>0.58</b>	
		S902916091	<b>0.58</b>	
		Acute	3.3	<0.8
Convalescent	ND	ND		
J <sup>d</sup>	05/02/2017	Acute	7.7	<0.8
		Convalescent	5.9	ND

<sup>a</sup> Assumed immunity is based on the manufacturer's normalized index value of  $\geq 1.1$  for positive mumps IgG antibodies.

<sup>b</sup> ND, not determined.

<sup>c</sup> Bold values indicate non-immune status.

<sup>d</sup> Unable to locate Patient J serum at repository.

**Table 3**  
Measles, mumps and rubella IgG seroprevalence.

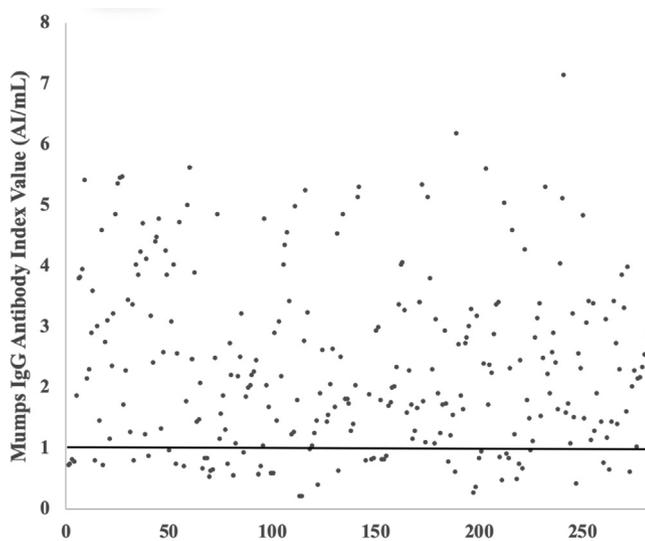
	Seronegative Index Values	
	Number <sup>a</sup>	Percentage
Mumps	36	12.2
Rubella	6	2
Measles	20	6.6
Mumps, Rubella	7	2.3
Mumps, Measles	9	3
Rubella, Measles	0	0
Mumps, Measles, Rubella	8	2.7
No seronegativity	213	71.2
Sum	299	100

<sup>a</sup> Number of serum samples demonstrating normalized index values below 1 for rubella and 1.1 for mumps and measles, per manufacturer's product insert.

Sequencing of RT-PCR viral samples determined that the strain was the genotype G strain. This was not surprising given genotype G has been implicated in other mumps outbreaks in the United States [8–10]. Together, our data suggests in those that contracted mumps, the current laboratory mumps IgG test may overstate protective immunity against the strain circulating during the outbreak. Regardless, all service members were given an additional MMR vaccination. Sera samples were submitted to the Center for Disease Control (CDC) for further investigation, including determination the extent antibodies derived from the mumps vaccine confers protection to non-vaccine strains by plaque reduction neutralization testing.

#### 4. Discussion

For outbreak control, the CDC recommends defining the populations at risk and rapidly vaccinating patients without presumptive evidence of immunity [6]. Every trainee in AIT had either two doses



**Fig. 1.** Distribution of mumps IgG antibody index among serum repository samples. Samples above the line are considered protective against mumps viral infection due to sufficient antibody concentrations.

of documented childhood MMR vaccination and/or serum drawn for measles and rubella serologies performed to infer MMR immunity. Our testing demonstrated 20.2% of pre-outbreak sera had IgG levels below what is considered protective for mumps, suggesting mumps immunity cannot be inferred from measles and rubella serology. In non-military settings (i.e. healthcare settings), policies may not indicate serological testing if childhood vaccination records are provided. Even if serological testing is performed, our data insinuates the utility of IgG titers may be less robust than once believed. This could signal a possible change in seroconversion ability, faster waning immunity than original seroconversion studies imply or the need for additional vaccine doses [11–13].

Before implementing a third MMR vaccine, the vaccine efficacy and the risk of adverse events were considered. In prior outbreak settings, adverse events were limited to mostly local injection site reactions that were less frequent than with the first or second MMR vaccines [14]. In an outbreak, targeted implementation of a third MMR vaccine has been shown to reduce attack rates [15]. A third vaccine may have helped curtail this outbreak, and is now recommended by the ACIP [16]. Waning immunity has been shown to contribute to mumps outbreaks [17]. With 20.2% of pre-outbreak sera below the antibody index value consistent with immunity, waning immunity likely contributed to the propagation of this outbreak but was not the main driver as the majority of individuals with confirmed mumps disease had sufficient IgG levels for ‘immune’ status and sera samples as great as ten years apart from the same individuals showed little decline in IgG levels and is consistent with previous studies [5,18,19].

The circulating mumps virus was identified to be genotype G by sequencing and typing. Although there are many genotypes, but only one known mumps serotype, the measured IgG values of our confirmed and probable mumps cases did not correlate to immunity [20]. Although laboratory testing of IgG levels suggests immune status according to normalize antibody index values or titers, there is no currently accepted serologic correlate of protection for mumps [21]. Of the seven confirmed and probable mumps cases, 72% (5/7) demonstrated IgG levels interpreted as protective from mumps. The current mumps component of the MMR vaccine administered in the U.S. is based on the live attenuated Jeryl-Lynn (JL) mumps strain, genotype A lineage 2 or 5 [22]. Cross-protection studies often disagree. One study acknowledges inter-strain antigenic variability, but still demonstrated a monotypic immune

response with antibodies raised against the JL vaccine strain and neutralization assays using a two other mumps strains, a genotype A and G strain [23]. Recent bioinformatics and sequencing suggests classification of genotypes is not enough and its the strain lineage that drives the viral epitope expressed and vaccine protection [24,25]. Hence, the biological reason for the low predictive value of immunity from measured IgG levels in our outbreaks may be due to the genetic variability of the genotype G lineage epitope leading to low neutralizing antibody specificities or the requirement for higher antibody concentrations needed in the sera required to neutralize the mumps virus circulating during our outbreak event [23,26,27]. For current laboratory methods, our data strongly suggests that mumps IgG testing is not a reliable surrogate for protection against all currently circulating mump lineages. Additional factors include the T-cell response since it is likely a significant determinate of immunity in the setting of a viral illness such as mumps, but it is difficult to measure by existing clinical laboratory methods [28]. Nonetheless, based on our data, IgG values are sub-optimal for assessing population-level immunity status. Changes to the markers defining mumps immunity, updated vaccine formulations, and policy changes are paramount for public health implications and prevention of the next mumps epidemics.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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### Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2019.08.054>.

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