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Incidence of mumps and immunity to measles, mumps and rubella among US military recruits, 2000–2004

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Summary Recent mumps outbreaks have evoked concerns of decreasing mumps immunity among adolescents and adults, including US military recruits subject to differing mumps immunization policies. To compare mumps incidence and to assess initial measles, mumps and rubella seropositivity, we conducted a cohort study among recruits from 2000 to 2004. Mumps incidence in the targeted MMR and universal MMR cohorts was 4.1 and 3.5 per 100,000 person-years, respectively, giving an incidence rate ratio of 1.16 ($P=0.67$). Measles, mumps, and rubella seropositivity was 84.6%, 89.5%, and 93.2%, respectively. Among recruits with measles and rubella immunity, 92.8% were mumps immune. These findings support the policy of targeting MMR immunization based upon measles and rubella serology alone.

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Introduction

The incidence of mumps decreased significantly in the United States following the recommendation for routine use of mumps vaccine in 1977 and the subsequent release of recommendations in 1989 and 1998 for administration of a two-dose series of MMR vaccine [1–3]. Despite these changes, outbreaks of mumps have continued to occur [4,5]. During recent outbreaks, a large proportion of

cases occurred among immunized individuals, suggesting the incomplete effectiveness of a two-dose series or the effects of waning immunity [5–7].

The seroprevalence of mumps antibody among adults has been investigated through several studies in populations subject to differing immunization recommendations. These studies found a broad range of mumps seropositivity among adults, ranging between 80% and 94% and varying with the year and age group studied [8–14]. Although high, the range of measured seropositivity generally falls below the 90–92% range thought necessary to interrupt sustained transmission of the virus [15]. Therefore, decreased immunity among adults may result in sufficient numbers of susceptibles to permit the occurrence of community-based outbreaks.

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US military recruits, as with other populations in school or camp settings, are placed in an environment particularly favorable to the rapid and efficient transmission of the mumps virus. In these high-risk settings, even high vaccination coverage may be insufficient to prevent mumps infection [6]. Although outbreaks of mumps among US military populations have been documented in the past, none have occurred in recent years following the release of recommendations for a two-dose series of MMR vaccine and the implementation of recruit MMR immunization [16,17]. Beginning in 1991, the military services implemented universal recruit immunization with a single dose of MMR vaccine, regardless of prior vaccination history [18]. Shortly thereafter, and informed by the results of population serosurveys, the Air Force transitioned to a policy of targeted MMR vaccination, limiting the administration of MMR vaccine to recruits lacking serologic evidence of immunity to measles or rubella [13,14]. With recent outbreaks of mumps, concerns have arisen that the practice of not specifically screening for mumps immunity in determining the need for MMR vaccine could lead to a relative increase in mumps risk among military recruits subject to screening. This concern led the Air Force to modify their accession immunization policy to include mumps screening and target MMR vaccination to recruits lacking immunity to measles, mumps, or rubella [19].

To provide data for senior decision makers to inform rational vaccination policy for the Department of Defense, the Army Medical Surveillance Activity was requested to perform a comprehensive retrospective cohort study of mumps incidence across the military services, and to quantify measles, mumps and rubella seropositivity among US military recruits entering service from 2000 to 2004.

Materials and method

Study population

The Defense Medical Surveillance System (DMSS) contains demographic, occupational, immunization, and medical encounter diagnosis data recorded during military service for active duty service members in the US military [20]. Using DMSS, we identified the cohort of all newly enlisted recruits, aged 17–35 years of age, who entered active duty in the US Air Force, Army, Navy, or Marine Corps between 1 January 2000 and 31 December 2004.

Incidence data

For analysis of incidence, a case of mumps was defined as the first coded medical encounter among a cohort member during the surveillance period resulting in a diagnosis of mumps (ICD-9CM 072.0-072.9). The surveillance period was from 1 January 2000 through 31 December 2004. Person-time at risk was calculated by summing the time from each subject's entry into the cohort to the end of the surveillance period or the occurrence of a censoring event. Censoring events (which would result in a change in risk of mumps or a loss of visibility in the DMSS) included post-accession MMR immunization, overseas deployment, termination of military service, change in status from Active to Reserve component

for 60 days or more, or a diagnosis of mumps. Demographic characteristics and rates of mumps diagnoses were compared between subjects in the US Air Force (the "targeted" group) and subjects in the US Army, Navy and Marine Corps (the "universal" group).

Laboratory samples

To evaluate serum antibody titers to measles, mumps, and rubella among the study cohort, we selected 3000 subjects who had a banked Military Entrance Processing Station (MEPS) serum specimen available for retrieval. These serum specimens are collected from all applicants prior to entry into military service for the purpose of HIV testing. The sera remaining after HIV testing is archived at the Department of Defense Serum Repository (DoDSR) where it is stored at -30°C [20].

Our sampling method selected equal numbers (750) of subjects from the following strata: targeted group foreign-born, targeted group US-born, universal group foreign-born, and universal group US-born. Within each of the strata, subjects were selected at random from among members of the study cohort with available serum. This methodology kept the distribution of other demographic characteristics similar to the entire cohort. In addition, the MEPS serum specimen or first available serum specimen prior to recruit MMR vaccination from the cases of mumps identified during the cohort analysis of incidence were selected for testing. When multiple MEPS specimens were available per subject, the most recent specimen was selected.

Serologic laboratory methods

Serum aliquots from the 3000 selected MEPS specimens and available serum specimens from the cases of mumps were sent to the Epidemiological Surveillance Division at the Air Force Institute of Operational Health (Brooks City Base, TX) for serologic testing. To assess IgG antibodies specific for measles, mumps and rubella, commercially available ELISA test kits (Measles Captia IgG ELISA, Mumps Captia IgG ELISA, and Rubella Captia IgG ELISA, Trinity Biotech, Jamestown, NY) were used according to manufacturer instructions. As reported by the manufacturer, the assays have a sensitivity of 99.3%, 99.3%, and 100% and a specificity of 91.0%, 96.6%, and 95.8% for measles, mumps and rubella, respectively. Qualitative results of immunity to each virus were reported. For all of the assays, an Immune Status Ratio (ISR) was calculated for each specimen (specimen optical density divided by the calibrator optical density). The ISR cutoff values for negative, equivocal, and positive results were ≤ 0.90 , $0.91-1.09$, and ≥ 1.10 , respectively. Equivocal results were re-tested and considered negative if the second test was equivocal or negative.

Statistical analysis

Comparisons of demographic characteristics between the targeted and universal groups were performed using a chi-square test for significance. For analysis of incidence rates (IR) and incidence rate ratios (IRR), a Poisson regres-

Table 1 Demographic characteristics of the groups receiving targeted MMR immunization ("targeted group") and universal MMR immunization ("universal group") at accession, 2000–2004

	Targeted group			Universal group		
	Total, <i>n</i>	%	Person-years (1000)	Total, <i>n</i>	%	Person-years (1000)
Total cohort	169,878	100	270	699,778	100	942
Age (years) ^a						
17–19	105,083	62	167	425,445	61	583
20–24	57,968	34	92	219,541	31	289
25–29	6,656	4	11	41,782	6	54
30–35	171	<1	0.3	13,010	2	16
Sex ^a						
Male	129,040	76	203	587,615	84	790
Female	40,838	24	67	112,163	16	152
Race–ethnicity ^a						
White	117,038	69	178	434,627	62	562
Black	25,662	15	43	114,322	16	162
Hispanic	10,017	6	20	79,268	11	119
Other/unknown	17,161	10	30	71,561	10	99
Marital status ^a						
Single	119,808	71	166	534,759	76	653
Married	46,364	27	97	157,944	23	278
Other/unknown	3,706	2	8	7,075	1	11
Years of education ^a						
9–10	1312	1	2	13,826	2	19
11–12	145,863	86	232	617,952	88	830
13+	21,563	13	35	65,376	9	90
Unknown	1,140	1	1	2,624	<1	3
Birthplace ^a						
United States	154,606	91	244	630,376	90	841
Foreign	14,129	8	24	67,822	10	97
Unknown	1,143	1	1	1,580	<1	1

^a $P < 0.001$ by chi-square.

sion model was used. Confidence intervals (95% CI) that did not include 1.0 and P -values ≤ 0.05 were considered statistically significant. STATA 8.0 (Stata Corp, College Station, TX, USA) was used for this portion of the analysis.

The results from the 3000 MEPS specimens were used for the analysis of seropositivity. The proportion of study subjects with a positive result for measles, mumps, or rubella IgG antibody was calculated. Logistic regression was used to calculate the odds ratio and 95% CI for measles, mumps, or

Table 2 Rates of mumps incidence in the total cohort and stratified by birthplace among the groups receiving targeted MMR immunization ("targeted group") and universal MMR immunization ("universal group") at accession, 2000–2004

	Incidence rate (per 100,000 person-years)	Incidence rate ratio (95% CI)	P -Value
Total cohort			
Universal group	3.5	1.16	0.67
Targeted group	4.1	(0.59–2.30)	
US-Born			
Universal group	3.7	0.89	0.77
Targeted group	3.3	(0.41–1.93)	
Foreign-born			
Universal group	2.1	6.00	0.05
Targeted group	12.4	(1.00–35.93)	

Table 3 Measles, mumps, and rubella seropositivity and odds ratios for seropositivity among study subjects and adjusted to the total recruit cohort, 2000–2004

	Total, <i>n</i>	Study subjects						Adjusted: total recruit cohort					
		Seropositive (%)			Odds ratio			Seropositive (%)			Odds ratio		
		Measles	Mumps	Rubella	Measles	Mumps	Rubella	Measles	Mumps	Rubella	Measles	Mumps	Rubella
Total	3000	86.1	91.6	94.8				84.6	89.5	93.2			
Sex													
Male	2369	85.9	91.2	94.4	1.00	1.00	1.00	84.7	89.0	93.0	1.00	1.00	1.00
Female	631	87.0	92.9	96.4	1.10	1.25	1.56	84.0	92.1	93.8	0.95	1.46	1.13
Age (years)													
17–19	1471	87.0	91.2	95.0	1.00	1.00	1.00	86.6	89.6	93.5	1.00	1.00	1.00
20–24	1197	84.8	92.7	94.9	0.83	1.23	0.99	82.2	91.6	94.0	0.72 ^a	1.27	1.09
25–29	265	86.4	88.7	95.8	0.95	0.75	1.22	84.6	81.3	92.6	0.85	0.51 ^a	0.88
30–35	67	88.1	89.6	86.6	1.10	0.82	0.34 ^b	78.5	78.4	73.0	0.57	0.42	0.19 ^c
Race–ethnicity													
White	1480	84.0	89.4	93.3	1.00	1.00	1.00	82.3	88.3	91.4	1.00	1.00	1.00
Black	489	91.4	95.1	97.5	2.03 ^c	2.30 ^c	2.85 ^c	90.3	93.7	97.3	2.00	1.98 ^a	3.32 ^b
Hispanic	459	86.9	93.9	97.2	1.27	1.83 ^b	2.46 ^c	88.2	89.1	97.0	1.60	1.08	3.08
Other/unknown	572	86.4	92.3	94.6	1.21	1.42 ^a	1.25 ^b	85.4	90.3	92.9	1.26	1.23	1.23 ^a
Education (years)													
9–10	38	94.7	86.8	92.1	1.00	1.00	1.00	92.0	86.5	95.1	1.00	1.00	1.00
11–12	2421	85.7	91.6	94.9	0.33	1.65	1.60	84.2	90.2	93.6	0.47	1.44	0.76
13+	538	87.2	91.8	94.6	0.38	1.70	1.50	85.5	85.7	89.8	0.52	0.94	0.45
Universal group	1500	85.7	91.5	94.5	1.00	1.00	1.00	84.4	89.3	92.8	1.00	1.00	1.00
US-born	750	85.1	90.3	94.7	1.00	1.00	1.00						
Foreign-born	750	88.0	93.1	95.7	1.29	1.45	1.26						
Targeted group	1500	86.5	91.7	95.2	1.08	1.03	1.16	85.3	90.5	94.8	1.07	1.14	1.40
US-born	750	84.1	88.8	92.4	1.00	1.00	1.00						
Foreign-born	750	87.2	94.1	96.5	1.29	2.02 ^c	2.29 ^c						

^a *P*-Value ≤ 0.05.^b *P*-Value ≤ 0.01.^c *P*-Value ≤ 0.001.

rubella seropositivity across demographic strata. To generate estimates of seropositivity and odds ratios for the entire recruit population, a weighted analysis was performed using the SURVEY LOGISTIC procedure of SAS 9.1 (SAS Institute, Cary, NC, USA) to account for the over-sampling of foreign-born recruits and Air Force personnel for the serologic testing.

Results

Cohort subjects and mumps incidence

The study cohort was comprised of 869,656 service members who contributed approximately 1.2 million person-years of follow-up. The universal group ($n=699,778$) was approximately four times larger than the targeted group ($n=169,878$). Demographic characteristics between groups were significant across all demographic strata, consistent

both with known differences between the military services and studies with large sample sizes (Table 1). There were 44 diagnoses of mumps in the study cohort, 11 in the targeted group and 33 in the universal group, during the 5 year surveillance period. The overall IR of mumps was 4.1 per 100,000 person-years in the targeted group and 3.5 per 100,000 person-years in the universal group (Table 2). The IRR between groups was not statistically significant ($IRR=1.16$, $P=0.67$). Among US-born service members, the IR of mumps did not significantly differ between the universal (IR: 3.7 per 100,000 person-years) and targeted (IR: 3.3 per 100,000 person-years) groups ($IRR=0.89$, $P=0.77$). Among foreign-born service members, the incidence rate of mumps was six times higher ($IRR=6.00$, $P=0.05$) in the targeted group (IR: 12.4 per 100,000 person-years) as compared to the universal group (IR: 2.1 per 100,000 person-years), but was just shy of statistical significance ($P=0.05$).

Table 4 Concordance of mumps seropositivity among study subjects seropositive to measles and rubella, study population and adjusted to the total recruit cohort, 2000–2004

	Measles and rubella seropositive subjects, <i>n</i>	Mumps concordant seropositivity (%)	
		Study subjects	Adjusted: total recruit cohort
Total	2438	94.2	92.8
Year			
2000	504	96.3	95.1
2001	470	95.7	96.6
2002	487	92.4	86.9
2003	496	93.5	93.0
2004	481	93.3	92.2
Sex			
Male	1915	94.1	92.4
Female	523	94.6	94.6
Age (years)			
17–19	1237	94.0	93.5
20–24	980	95.2	93.5
25–29	221	90.5	84.4
30–35	53	96.2	91.2
Race–ethnicity			
White	1173	92.8	92.5
Black	421	96.1	94.4
Hispanic	382	95.1	90.6
Other/unknown	462	95.4	93.5
Education (years)			
9–10	33	90.9	89.6
11–12	1982	94.1	93.3
13+	420	94.9	89.9
Targeted	1251	94.3	93.6
US-born	628	93.5	
Foreign-born	623	95.0	
Universal	1187	94.2	92.6
US-born	607	92.2	
Foreign-born	580	96.1	

The majority of mumps cases occurred in the US, however 7 were seen at medical treatment facilities outside of the US: 4 in Germany, 2 in Japan, and 1 in Spain. Mumps cases were primarily diagnosed during an outpatient visit, however 6 of the cases resulted in a hospitalization. The cases ranged in age at diagnosis from 18 to 30 years with a mean and median age at diagnosis of 21. Out of the 44 cases of mumps, 43 had available MEPS or pre-MMR vaccination specimens. Two, four, and one of the tested specimens were seronegative for mumps, measles, and rubella antibody, respectively. No cases were seronegative to more than one of the antigens. The two cases seronegative for mumps antibody were both US-born and from the universal group. Time since collection of the specimen to diagnosis of mumps ranged from 80 to 1400 days, with a mean of 542 days. Twenty-four of the cases received an MMR immunization after accession but prior to diagnosis of mumps.

MMR seropositivity

Measles, mumps, and rubella seroprevalence data among the study subjects and adjusted to the total cohort are presented in Table 3. Measles, mumps and rubella seropositivity among study subjects was 86.1, 91.6, and 94.8, respectively. The adjusted measles, mumps, and rubella seropositivity was only slightly lower at 84.6, 89.5, and 93.2, respectively. A higher proportion of foreign-born recruits were seropositive for measles, mumps, and rubella antibody as compared to US-born recruits, although this difference was only statistically significant for mumps and rubella between study subjects in the universal group (OR = 2.02 and 2.29, respectively, $P \leq 0.001$). In adjusted analysis, measles seropositivity among 20–24 year olds, mumps seropositivity among 25–29 year olds, and rubella seropositivity among 30–35 year olds were significantly lower as compared to 17–19 year olds ($P \leq 0.05$, 0.05, and 0.001, respectively). The odds of being seropositive for mumps antibody among blacks and seropositive for rubella antibody among blacks and other/unknown race–ethnicities were significantly higher as compared to whites in the adjusted analysis ($P \leq 0.05$, 0.01, and 0.05, respectively).

There were 29 subjects seronegative to all three viruses. These recruits ranged in age from 18 to 31 years of age, with a median age of 19. Approximately 25% of these recruits were foreign-born. All other demographic characteristics for these seronegative recruits had a similar distribution as the entire 3000 recruits that were tested.

The percentage of subjects with concordant mumps seropositivity, given immunity to measles and rubella, are presented in Table 4. Concordant measles and rubella seropositivity was highly predictive of mumps immunity among all four study groups: 95.0%, 93.5%, 96.1%, and 92.2% for the targeted foreign- and US-born, and universal foreign- and US-born study groups, respectively. When the results were adjusted to estimate the total recruit population, all strata except 25–29 year olds and those with 9–10 or 13+ years of education had over 90% mumps seropositivity concordance with measles and rubella. From 2000 to 2004, the adjusted mumps seropositivity given measles and rubella seropositivity remained above 92%, with the exception of 2002 where the proportion dropped to 87%.

Discussion

This large seroepidemiology study is one of the few studies to investigate susceptibility to measles, mumps, and rubella among the young adult US population several years after recommendations for a two-dose MMR schedule and during a time of increasingly frequent outbreaks of mumps. In addition, this is the only recent study to our knowledge to investigate measles, mumps, and rubella seroprevalence and mumps incidence among recruits across all four services of the US military. The recruit population represents a diverse sample of the US young adult population and results from this population may provide better insight into the seroprevalence of measles, mumps, and rubella antibody in the general US young adult population.

Previous serosurveys of service-specific recruit populations have reported measles, mumps, and rubella seropositivity in the range of 80–85%, 85–88%, 83–90%, respectively [11–13]. Our findings of slightly higher seroprevalence are not unexpected. Previous studies were conducted at the time of or shortly following the release of recommendations for a two-dose MMR schedule, and therefore would not have reflected the population effect of this second dose. A majority of the recruits in our cohort were expected to have received a second dose of MMR as a catch-up, and therefore a higher proportion were anticipated to be seropositive for measles, mumps, and rubella antibody. Differences between our findings and those of previous reports may also be due in part to differences in the assays used to determine seroprevalence. For example, although the reported specificity of the mumps assay is high, 96.6%, there is the possibility for false-positives to have occurred.

We observed decreasing seropositivity to measles, mumps, and rubella with age. This may be due to a combination of causes, including cohort effects. Older subjects may have been less likely to have received a second dose of MMR and therefore would be less likely to be seropositive [21]. Additionally, it is possible the decreasing seropositivity reflects waning immunity consistent with a greater number of years elapsed since last immunization. Previous studies of mumps outbreaks investigating whether waning immunity or primary vaccine failure were contributing factors have reported conflicting results. Most studies were conducted when only one dose of MMR was recommended [22–24]. A more recent study evaluating children receiving two doses of MMR noted a decrease in mumps protection with increasing age, suggested waning immunity may have occurred [7]. In our study, this effect may have been minimized, because one would expect the older age group to have been exposed to wild virus as a child before routine mumps recommendations came into effect, which may have increased the seropositivity in this age group. Investigations of waning immunity after vaccination may be better investigated in a population with minimal to no wild virus exposure. With outbreaks of mumps occurring in the US and around the world, decreasing levels of mumps antibody may be a contributing factor, whether produced through primary vaccine failure or waning immunity. As vaccination histories on our population prior to accession were unavailable, we were unable to investigate the effects of time elapsed since last vaccination or number of prior MMR doses to better determine the cause of this age effect. As noted by others, our findings do support continued

investigation during outbreaks to look for waning immunity [6].

The high measles, mumps, and rubella seropositivity among incoming recruits supports the serological screening policies implemented in the 1990s by the US Air Force and also those of the newly adopted Army Accession Screening and Immunization Program (ASIP) [25,26]. Our study demonstrates that basing the need for MMR immunization on results of measles and rubella serologic screening would result in only 4–8% of the recruit population remaining potentially susceptible to mumps. This small percentage, distributed over the entire military population, is less than the 8–10% population susceptibility thought necessary for sustained population mumps transmission and should not, in ordinary settings, result in additional mumps cases [15]. This assumption has been further supported by the results of our 5-year cohort study, which demonstrated that such a targeted MMR vaccination policy resulted in no statistically significant increase in the rate of mumps as compared to a policy of universal MMR immunization.

Among the foreign-born recruit population we found somewhat inconsistent findings. In the cohort analysis, foreign-born recruits had 6 times the risk of mumps comparing the targeted cohort to the universal cohort, although this difference was not statistically significant. Conversely, the serosurvey found that foreign-born recruits, as a population, had slightly higher mumps seropositivity and slightly higher concordant mumps seropositivity than US-born recruits. Since the confidence intervals of the IRR were very wide and included 1.0, it is possible the foreign-born recruits in the targeted cohort did not have an elevated risk of mumps over the universal group, which would be more consistent with the serologic findings. However, if there truly is an elevated risk as the point estimate shows, other reasons may explain this apparent conflict between the incidence data and the serology data. One possible explanation is that total mumps IgG does not necessarily correlate with protection from mumps infection [21]. An alternative explanation is that the foreign-born recruit population on a whole demonstrated slightly higher seropositivity attributable to the continued circulation of wild virus in their birth country, childhood or adolescent vaccination, and/or revaccination upon immigration. Such an explanation would permit the possibility of sub-populations never receiving mumps immunization in the US, including those having received only measles rubella (MR) vaccine in foreign countries, thus remaining highly susceptible to mumps. Supporting this hypothesis is a study among Canadian immigrants who were never immunized upon immigration, which found 36% of the population to be susceptible to at least one of the MMR viruses [27]. However, the serologic results from the pre-accession sera for the mumps cases, found all foreign-born cases to be mumps seropositive. Therefore, it is plausible that either total mumps IgG did not correlate with mumps protection or mumps immunity waned below protective titers during the average of 1.4 years from the time of the pre-accession blood draw to the mumps infection.

Our study has found relatively high seroprevalence of measles, mumps, and rubella antibody among US military recruits, and strong concordance between mumps seropositivity with measles and rubella seropositivity. Based on these findings, we believe the US military services are justified

in implementing a policy of screening recruits for measles and rubella immunity alone and basing the decision to vaccinate with MMR-based solely on these findings. This approach should not only prove cost-saving, but will minimize redundant immunization of recruits with live-virus vaccine. Our findings suggest that foreign-born populations may represent a population at higher risk of mumps, and further investigation of this group is necessary to determine whether specific mumps vaccination policies for foreign-born recruits should be developed to ensure their adequate protection.

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