Defense Health Board Report

May 18, 2020

Measles, Mumps, and Rubella Booster Immunization Practices

OFFICE OF THE ASSISTANT SECRETARY OF DEFENSE
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DEFENSE
HEALTH
BOARD

MEMORANDUM FOR ASSISTANT SECRETARY OF DEFENSE FOR HEALTH AFFAIRS

SUBJECT: Measles, Mumps, and Rubella Booster Immunization Practices

The Defense Health Board (DHB) is pleased to submit its report and its accompanying findings and recommendations from its independent review of the Department's Measles, Mumps, and Rubella (MMR) Booster Immunization Practices. In the midst of the COVID-19 pandemic, the parallels between mumps and SARS-CoV-19 in their operational impact, our dependency on an effective vaccine, and the imperfections of testing were not lost on the Board.

On November 7, 2019, the Assistant Secretary of Defense for Health Affairs (ASD(HA)) directed that the DHB, through its Public Health Subcommittee, provide recommendations to the Department on the optimal way to minimize the risk of mumps in our armed forces and maintain medical readiness. Specifically, the ASD(HA) requested the DHB to:

- Determine the risk of mumps infection in Service members
- Inform DoD policy regarding the need for either selective or universal MMR boosters

The Public Health Subcommittee reviewed the literature and epidemiology to quantify the risk of mumps outbreaks to readiness; to determine if current immunization policies are sufficient to mitigate those risks and, if not, recommend best practices to mitigate them; and to provide any additional recommendations to inform policy. The Subcommittee received briefings from, and consulted with, experts from both government and civilian institutions.

The Public Health Subcommittee presented to the DHB on May 18, 2020 and, following public deliberation of the findings and recommendations, the attached report was approved and finalized. The key and first recommendation is for universal booster, or "third," MMR immunization closer in time to a Service member's time in service. The Board leaves determination of which recruits and Service members have or have not received the two CDC-recommended MMR doses previously to the Department and individual Services.

On behalf of the Board, I appreciate the opportunity to provide the Department with this independent review and hope that it provides useful information to reduce the risk of mumps infection to the readiness of Service members.

Jeremy Lazarus, M.D.
President, Defense Health Board

Attachment:
As stated

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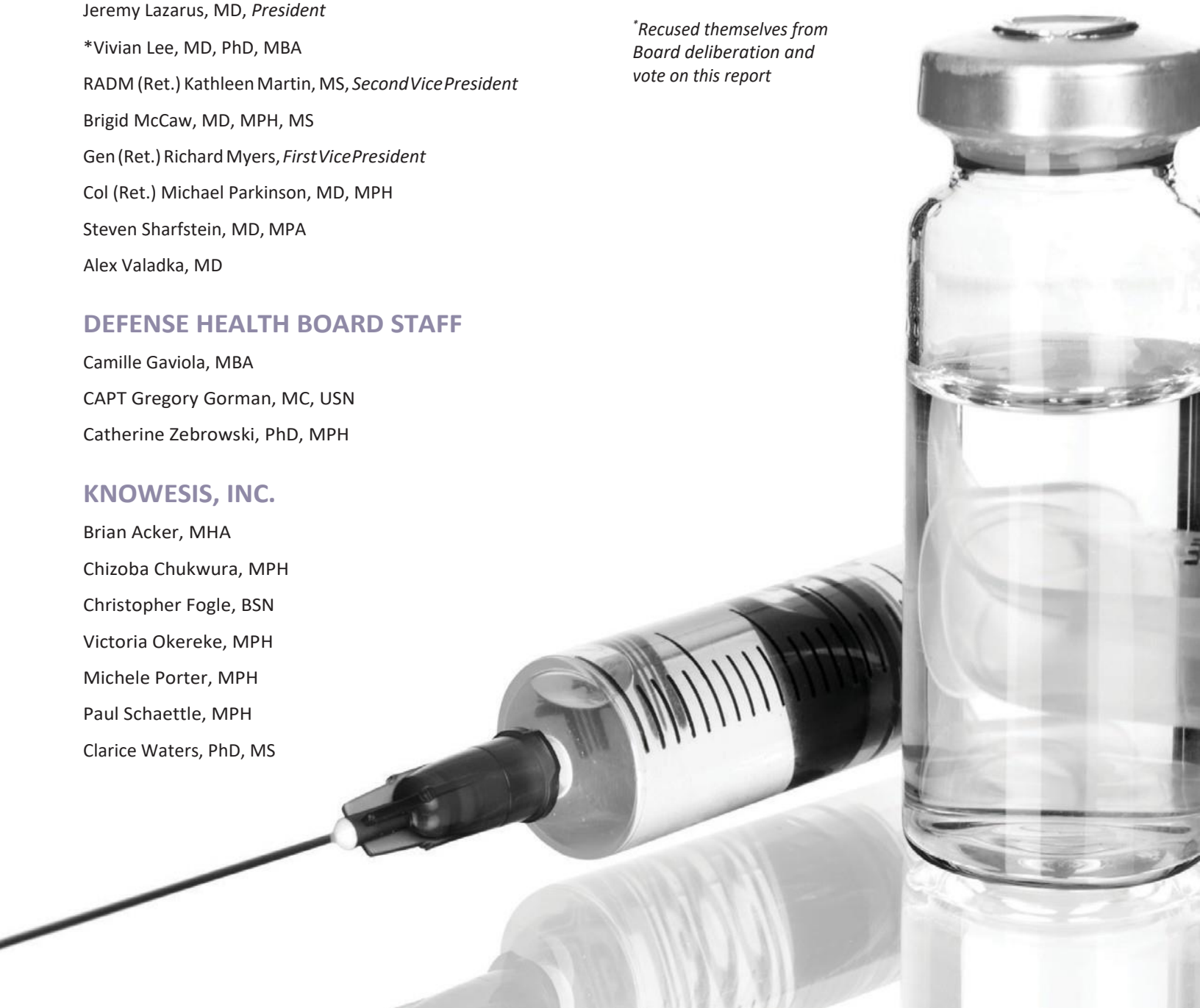

Executive Summary

Reported cases of mumps infection in the United States (U.S.) have dropped since the introduction of the single-component mumps vaccine in 1967. After introduction of the multi-component measles, mumps, rubella (MMR) vaccine, cases in the U.S. and worldwide fell to the point where the International Task Force for Disease Eradication identified mumps for eventual global eradication. By 1991, all military recruits received an MMR vaccine. By 2010, the Department of Defense (DoD) had adopted a policy of immunizing recruits with MMR vaccine only if their antibody titers to measles or rubella had dropped below threshold levels established by the commercial testing laboratories as indicative of immunity. As part of a 2010 Defense Health Board (DHB) review of MMR immunization practices by the Department of the Navy, the DHB recommended that the Navy continue the practice of MMR immunization based on serosurveillance, but that universal MMR vaccination be re-instituted in the event of an increased risk of a mumps outbreak.

Since the 2010 DHB report, there has been an increase in the incidence of mumps in the U.S. Mumps continues to be endemic in some areas of the world where the Military Services have a long-term presence. There is a lack of global emphasis on administration of mumps vaccines, and there have been recent outbreaks on board U.S. naval vessels and within ground units of the U.S. military. These mumps outbreaks put both military and civilian personnel at risk, are financially costly, disrupt the mission, and potentially compromise unit readiness. The individual Services have diverged in their MMR immunization practices over the years based on their experiences with mumps outbreaks, with the Navy changing their policy as recently as April of 2019.

On November 7, 2019, the Assistant Secretary of Defense for Health Affairs (ASD(HA)) directed that the DHB, through its Public Health Subcommittee, provide recommendations to the DoD on the optimal way to minimize the risk of mumps in our Military Services and maintain medical readiness. In this request, the Public Health Subcommittee was directed to review scientific literature and epidemiologic trends in order to quantify current and future risks to medical readiness from mumps outbreaks; to determine if current immunization policies are sufficient to mitigate potential risks and, if not, recommend best practices to mitigate those risks; and to provide any additional recommendations to inform policy, such as impact to budgetary and logistical requirements. The Public Health Subcommittee received briefings from, and consulted with, a variety of subject matter experts from both government and civilian institutions.

For this report, the DHB adopted guiding principles to frame the review, findings, and recommendations. First, the objective of this tasking is to minimize – not eliminate – the risk of mumps to the readiness of the Military Services. Second, the readiness costs to the DoD of an outbreak of mumps and other infectious diseases can include loss of critical operational capacity, and thus is more than the traditional measurable or estimated financial costs of vaccines, laboratory testing, medications, and individual personnel hours. Lastly, the DoD should generally follow the recommendation of the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices. However, it is important to acknowledge that there may be military-specific considerations when operational readiness may dictate an alternate course of action. Therefore, the resulting report focuses on 1) the impact of mumps outbreaks on military readiness; 2) current use and limitations of the MMR vaccine; 3) use of serologic testing as a surrogate for immunity to mumps; 4) safety and efficacy of a booster dose, or third dose, of MMR vaccine; and 5) military cost considerations for administration of the MMR vaccine.

The topic of infectious disease prevention in deploying Service members is an important one. In this review, the DHB has reconsidered the administration of a booster dose, or third dose, of MMR vaccine at Basic Military Training as a means of minimizing the risk of mumps to the readiness of the Military Services. Receipt of two childhood doses of MMR, documented for recruits directly through records or through the application of DoD policy of assuming immunization receipt based on screening, provides a foundation for mumps infection protection. The recommendations listed below reflect our current understanding of the situation based on the information available.

FINDINGS

1. **Outbreaks of mumps can have a significant impact on military readiness.**

   Despite the current DoD practice of directly or indirectly screening for antibodies to mumps and boosting recruits with low mumps titers, there have been recent outbreaks on board U.S. naval vessels and within ground units of the U.S. military that put both military and civilian personnel at risk, are financially costly, disrupt the mission, and potentially compromise unit readiness.

2. **Two doses of the MMR vaccine reduce the risk of developing mumps infections, but protection is not complete.**

   Despite relatively high mumps vaccine rates, there have been recent large-scale outbreaks of mumps in the U.S.

3. **There is no reliable laboratory surrogate of protection against mumps infection. The presence or absence of antibodies against the mumps virus detected with current methodologies is not a reliable indicator of protection or future susceptibility to mumps infection.**

   There is discordance between mumps antibody titers, as determined by enzyme linked immunosorbent assay or plaque reduction neutralization, and protection. There are numerous examples where groups with high anti-mumps titers are susceptible to infection while others with low anti-mumps titers are resistant. The loss of mumps protection is best correlated with time since last immunization. This is reflected by a waning humoral and cellular immune response (the latter not well delineated, which may account in part for the discordance between antibody titers and protection), individual genetic differences in immune responses, and antigenic differences in circulating wild-type virus strain (genotype G) and vaccine virus strain (genotype A).

4. **Administration of a third MMR vaccine dose offers an additional margin of protection against mumps infection. At present, this is only available for those older than 18 years of age through administration of the trivalent MMR vaccine.**

   Epidemiologic studies reported lower attack rates among persons who received the third dose during the outbreak compared with persons who had received 2 doses before the outbreak. Following the institution of a routine third dose at the time of enlistment, the Korean Armed Forces reported a 3-year decrease in the incidence of mumps in military personnel.

RECOMMENDATIONS

1. **Immunization strategy for new recruits:**

   Administer one dose of MMR vaccine to all new recruits regardless of their previously documented immunization history (e.g., immunization records). Administer another dose of MMR vaccine one month later for recruits who had zero or only one documented MMR vaccination prior to entering the DoD. The DoD should continue to follow CDC guidelines for individuals with a contraindication for use of the MMR vaccine.

2. **Immunization strategy for other Service members who have not received a documented 3 doses:**

   Administer one dose of MMR vaccine to:

   - Service members assigned to bases in host countries with endemic mumps, as determined by the Centers for Disease Control and Prevention
   - Service members assigned to submarines or other units to be deployed for an extended period of time without access to regular communication, without logistical support in the event of a mumps outbreak, or in times of significant conflict

   This does not prescribe or prohibit the use of an outbreak dose should circumstances warrant.

3. **Family member screening to protect Service members overseas**

   Ensure family members older than 4 years of age who are accompanying Service members to countries with endemic mumps have received the CDC recommended 2 doses of MMR vaccine, unless the family member can provide documentation for a medical exemption.

4. **Inclusion of mumps vaccine research as a DoD research priority**

   The DoD should establish intramural or extramural research programs to help develop a monovalent genotype G mumps vaccine or mumps vaccine against all genotypes, identify correlates of protective immunity, and better define the duration of protection.

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INTRODUCTION

In a memorandum dated November 7, 2019, the Assistant Secretary of Defense for Health Affairs (ASD(HA)) directed that the Defense Health Board (DHB) provide recommendations to the Department of Defense (DoD) on the optimal way to minimize the risk of mumps in our armed forces and maintain medical readiness. The ASD(HA) asked the DHB to address and develop findings and recommendations on the policies and practices in place to determine the risk of mumps infection in Service members and to inform DoD policy regarding the need for either selective or universal Measles, Mumps, Rubella (MMR) vaccine booster immunizations.

The ASD(HA) charged the DHB to determine if universal administration of MMR vaccine to Service members upon entrance into the military and a booster vaccine for current Service members is warranted in light of recent mumps outbreaks and effects on readiness. Specifically, the DHB's Public Health Subcommittee should:

- Review scientific literature and epidemiologic trends to quantify current and future risks to medical readiness from mumps outbreaks.
- Determine if current immunization policies are sufficient to mitigate potential risks and, if not, recommend best practices to mitigate those risks.
- Provide any additional recommendations to inform policy, such as impact to budgetary and logistical requirements.

The Subcommittee met in person on February 24-25, 2020, and by video teleconference on March 17, 2020, March 31, 2020, April 14, 2020, April 21, 2020, April 28, 2020, and May 5, 2020. The Public Health Subcommittee examined mumps epidemiology, the current state of mumps immunologic testing, mumps vaccines, and current military and civilian practices for prevention of mumps infection.


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THE IMPACT OF MUMPS ON MILITARY READINESS

In 2010, the Department of the Navy requested that the DHB conduct a review of their MMR immunization practices. A specific issue at that time was whether or not a universal MMR immunization was needed during the Navy's Accessions Screening and Immunization Program (ASIP).[1] The Department of the Navy noted large-scale outbreaks from 2006-2009 despite relatively high mumps vaccine coverage rates. Costs and frequency of vaccination were also a consideration. After a thorough review, the DHB recommended that the Navy continue then-current ASIP practices. Under ASIP, the Navy administers the MMR vaccine solely to eligible recruits who demonstrate a lack of adequate immunity (i.e., antibodies) to mumps following serological screening. At the time, the DHB did not recommend administration of a third dose of MMR vaccine after accessions. The DHB recommended that universal MMR vaccination would be re-instituted in the event of an increased risk of a mumps outbreak.

At present, current practices for MMR immunization of recruits at Basic Military Training (BMT) vary between the Services. Army recruits are screened for the presence of antibodies to measles and rubella. Individuals who have measles- or rubella-specific immunoglobulin G that is detectable by any commonly used serological assay are considered to have adequate laboratory evidence of measles or rubella immunity. Laboratory evidence of measles or rubella immunity is used by the Army as proxy-measures for mumps immunity. Air Force, Navy and Marine recruits are similarly screened for measles and rubella antibodies and also for the presence of antibodies to the mumps virus. For all Services at BMT, individual Service members lacking evidence of antibodies to measles, mumps, or rubella are vaccinated with MMR vaccine. There are other vaccines for infectious diseases that recruits receive at BMT without prerequisite serologic testing. According to the DoD publication on Immunizations and Chemoprophylaxis for the Prevention of Infectious Diseases, recruits are assumed to have received the basic immunizing series for tetanus, diphtheria, acellular pertussis (i.e., Tdap) and polio unless there is reason to suspect that childhood vaccines may not have been administered.[2] Thus, the majority of new recruits could be assumed - using the same screening criteria - to have received two doses of the MMR vaccine on the CDC prescribed schedule. At the time of the writing of this report, a revision of the joint instruction on immunization and chemoprophylaxis against infectious diseases is underway.

Immunization programs for the Military Services aim to prevent vaccine-preventable diseases. In MMR vaccinated individuals, mumps causes mild morbidity and is rarely fatal. A Service member with mumps illness would likely be 'Sick in Quarters' for 3-4 days in terms of being able to perform their duties[3]; this does not include additional time not performing duties in order to prevent the spread of mumps to others. Mumps is highly infectious. The R-naught (R_0) of mumps, the average number of new infections transmitted by an infected individual, is 4-7.[4] This is approximately 2-3 times the estimated R_0 of influenza and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[5,6] Individuals can transmit the virus up to 11 days after exposure. Asymptomatic individuals can transmit the virus up to a week before becoming symptomatic.[7] These factors cause a mumps outbreak to decrease readiness at the unit level by increasing the risk that a significant percentage of a unit could simultaneously be ill for many weeks – a significant disruption to operational readiness. The need for isolation, logistics for transporting MMR vaccine through a cold-chain, and avoidance of negative publicity from transmitting an infectious disease to host-nation nationals are additional considerations that reflect the impact of a mumps outbreak on the readiness of a military unit.

Despite the current DoD practice of directly or indirectly screening for antibodies to mumps and boosting recruits with low mumps titers, there have been recent outbreaks on board U.S. naval vessels and within ground units of the U.S. military that put both military and civilian personnel at risk, are financially costly, disrupt the mission, and potentially compromise unit readiness. Examples include:

- **2017 Advanced Individual Training (AIT) at Fort Sam Houston:** In April 2017, five Army Soldiers assigned to Advanced Individual Training (AIT) were admitted to Brooke Army Medical Center with parotitis and suspected mumps; three were diagnosed with mumps by real-time reverse-transcription polymerase chain reaction (rRT-PCR).[8] Contact tracing identified four additional confirmed and two presumptive cases of mumps. The probable source of the outbreak was traced to a Soldier who had likely contracted mumps in another state during BMT and had been admitted with undiagnosed parotitis in late February 2017. Army Public Health Nursing administered an outbreak dose of MMR vaccine to the entire AIT population at Fort Sam Houston of 420 Soldiers. There were no additional cases of mumps.

- **2019 USS FORT MCHENRY:** In late November 2018, a Marine was exposed to mumps, likely from a civilian in North Carolina.[9] The Marine embarked on the USS FORT MCHENRY in mid-December 2018 and shortly thereafter presented to the ship's medical personnel with unilateral parotitis. By mid-January 2019, an additional five Marines presented with parotitis. The ship was in a remote area within the U.S. Central Command region and there was no ability to test for mumps infection or administer an MMR vaccine on board. The Navy Environmental and Preventive Medicine Unit flew in and boarded the ship to give an MMR vaccine outbreak dose to each crew member. The command made the decision to cancel port calls and Marine exercises until 4 weeks after the last case. From January to April there were 28 confirmed cases diagnosed aboard the ship. Twenty (71%) of the cases were Marines and 17 (61%) of the cases had received an MMR vaccine outbreak dose; four of the 17 were diagnosed over 28 days after receiving the outbreak dose. In mid-May, Navy Central Command, in consultation with the Navy Marine Corps Public Health Center and the Navy Central Command Surgeon, cleared the ship from quarantine, although special country clearances for port calls had to be obtained. Essentially, the USS FORT MCHENRY and the embarked Marines were not fully operational for four months.[9]

- **2019 173rd Airborne Brigade at Vicenza:** In July 2019, a Soldier assigned to the 173rd Airborne Brigade in Vicenza, Italy was treated for parotitis at a local Italian hospital. Lab tests reported a positive mumps immunoglobulin M (IgM) antibody (an indicator of ongoing or recent infection), prompting the Army Public Health Nurses at Vicenza to review previous encounters for similar cases. They identified nine Soldiers in the unit with suspected mumps over the previous two months.[10] Only three had been tested for mumps. Simultaneously, the Battalion Commander fell ill and was diagnosed with mumps while attending a meeting of military leaders in Germany. In total, there were 10 confirmed or suspected cases, two identified clinically and the rest retrospectively. The 10 Soldiers were isolated for five days and prevented from traveling with their unit for a training exercise. Two hundred Soldiers in the battalion and 175 individuals who had contact with the Battalion Commander in Germany received one outbreak dose of MMR vaccine. There were no additional cases.[10]

  The Soldier, who was the index case initially seeking health care at the host-nation hospital, complicated this outbreak in Vicenza. Italy has endemic mumps and does not track mumps cases. Further, rRT-PCR is not readily available for diagnosis in local laboratories.[10]

- **Pacific-based warship and submarine:** In October 2019, four Sailors from a Pacific fleet Navy ship presented with bilateral parotitis at the time of confirmed mumps cases in the community.[9] The warship left for a planned 5-week mission without the four suspected mumps cases aboard. Out of an abundance of caution, preventive medicine teams vaccinated all members of the ship and other personnel aboard with MMR vaccine. There were no additional cases and the ship deployed on schedule. Because of the early intervention, this event had no impact on their operational readiness.

  A similar situation for a Pacific-coast based submarine occurred when an individual, who frequently boards submarines while in port, was diagnosed with bilateral parotitis 72 hours after his last visit to the submarine. The

submarine embarked and was unable to receive communications to warn about the potential exposure. Given the high-risk environment and the potential exposure, Military Public Health officials administered an outbreak dose of MMR vaccine to the crew, although that intervention was delayed until radio contact with the submarine could be made and the logistics needed to provide the supplies to the boat at their next port of call could be arranged.[9] There were no parotitis or mumps cases among the crew.

In 2018, the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices recommended a third dose of mumps-containing vaccine for persons previously vaccinated twice with mumps-containing vaccine who are identified by public health officials as at increased risk for mumps because of an outbreak.[11]

As part of the 2010 DHB review of MMR immunization practices by the DoD, the DHB recommended that universal MMR vaccination be re-instituted in the event of an increased risk of a mumps outbreak. Since the 2010 DHB report, there has been an increase in the incidence of mumps in the U.S. Mumps continues to be endemic in some areas of the world where the Military Services have a long-term presence, and there is a lack of global emphasis on administration of mumps vaccines. Recent outbreaks pose potential threats to operational readiness in military units. Consequently, in this review, the DHB has reconsidered the administration of a booster dose, or third dose, of MMR vaccine at BMT as a means of minimizing the risk of mumps to the readiness of the Military Services.

CURRENT USE AND LIMITATIONS OF MUMPS VACCINE

The CDC recommends universal immunization with the MMR vaccine in order to reduce measles, mumps, and rubella disease severity and outbreaks. The protective efficacy of the MMR vaccine for mumps is 78% after one dose and 88% after two doses. This had resulted in a 99% reduction in the incidence of mumps in the U.S..[12] Additionally, for those who do develop mumps after one or two vaccinations, the rate of serious complications is significantly lower than among those who were not vaccinated.[13] However, despite relatively high mumps vaccination rates, there have been recent large-scale outbreaks of mumps in the U.S.. In 2006, after six years of fewer than 350 cases per year, outbreaks throughout the U.S. led to over 6,500 reported cases.[14] There have been between 1,233-6,366 cases in the U.S. each year since 2014. Moreover, asymptomatic infection can occur in 20-40% of infected individuals and symptomatic cases may not be diagnosed as mumps.[3,15] There are several possible explanations for this phenomenon:

- There are 12 different genotypes of mumps virus. The genotype G mumps virus strain is the most common genotype identified and has accounted for more than 98% of the cases in the U.S. since 2006.[16] Of note, the mumps vaccine currently in use in the U.S. contains a live, attenuated virus and is based on the genotype A virus. It is not clear if the difference between the strain of the virus used in the vaccine and the strain that predominates in natural infections plays a role in the increase in the number of cases of mumps. Different strains are prevalent in different parts of the world.[17-19]

- The mumps vaccine is typically administered as a component of an MMR vaccine. There is no commercially available single-component mumps vaccine in the U.S. and no available vaccine based on the genotype G strain that is predominant in the U.S..

- The mumps component of the MMR vaccine has the highest rate of waning immunity among the three components. Multiple studies document decreases in mumps-specific antibodies over time.[20-22] Analyses of longitudinal serum samples from Service members document a non-linear decrease in antibody levels, with a marked decrease 13 years after the most recently administered MMR vaccine.[23] Consequently, if the second dose of MMR vaccine is administered at the recommended 4-6 years of age, individuals entering the armed forces at 18-19 years of age are entering a period of decreasing antibody titers and, based on time from last immunization, decreasing protection.

- While the mumps protective efficacy of the MMR vaccine is 78% after one dose and 88% after two doses, the documented range of protection is 49%-92% following one dose and 31%-95% following a second dose.[24] This indicates that there are a number of individuals who receive one or two doses of vaccine who are not protected.

- Under-recognition, asymptomatic cases, and reliance on diagnostic codes for retrospective identification of mumps infection in military personnel likely under-estimates the current burden of mumps in the armed forces. Possible cases in the DoD equaled or exceeded confirmed cases in 8 of the last 10 years.[25]

- The standard for diagnosing mumps is to detect mumps-virus ribonucleic acid (RNA) by nucleic acid testing using the rRT-PCR. Individual vaccination status does not affect rRT-PCR testing. To optimize accuracy, the specimen needs to be collected within three days after the onset of parotitis.[26] Following this time, levels of viral RNA decline and the test may not be adequately sensitive.[27] Further complicating the ability to make a confirmed diagnosis, patients may not present within this window of time and clinicians may not be aware of proper specimen collection techniques. In addition to the use of nucleic acid testing, detecting an anti-mumps virus IgM antibody response is diagnostic of current or recent mumps infection or vaccination.

- Social and environmental factors unique to the military, including close quarters housing, extended deployments with limited access to communications and logistical support should an outbreak occur, and deployment to host countries with endemic mumps, also contribute to mumps transmission.

LIMITATIONS OF SEROLOGIC TESTING FOR IMMUNITY TO MUMPS

The key objective for immunization is protection against natural infection. Protection is commonly defined by determining the efficacy of a vaccine: the percentage reduction of infection in vaccinated versus unvaccinated individuals. Immunologic responses to mumps, through either natural exposure or vaccination, are not synonymous with protection against mumps infection.

The sensitivity and specificity of the assays used to measure antibodies to mumps virus vary and include measurement of total levels of antibodies with an enzyme linked immunosorbent assay (ELISA) and levels of neutralizing antibodies with a plaque reduction neutralization (PRN) assay. Assays detect various virus strains differently and each laboratory defines its own standards for what constitutes a positive test outcome. It has been suggested that levels of neutralizing antibodies directed against the genotype G mumps virus in the PRN assay may be the best correlate of protection against mumps infection, but this assay has not been validated as a metric of protection.[28] Moreover, the assays for neutralizing antibody are expensive and take 5-7 days compared to the ELISA which is less expensive and can be performed in a day. Importantly, there is no clearly established correlation between threshold levels of antibody as determined by ELISA or the PRN assay and protection from mumps. While many bacterial and viral vaccines have well-defined immune function levels as correlates of protection, several vaccines, such as vaccines for zoster, tuberculosis, and mumps, lack a correlate of protection.[15]

The nature of the T-cell response to mumps infection or immunization is unclear. Given that mumps is a viral infection and the vaccines contain live, attenuated viruses, it is likely that the body generates both CD4 and CD8 T-cell responses which play a role in protective immunity. This may also explain some of the difficulty in determining the level of antibody that correlates with protection. Tests for cell-mediated immunity are expensive and labor-intensive; these include skin tests, T-cell stimulation and proliferation indices in the presence of mumps antigen, mumps-specific CD4 T-cells expression of CD69, and production of interferon-γ and other cytokines.[29] These assays are not practical for evaluation of immune status.

To reiterate, mumps specific antibodies are indicative of an immunologic response to either the vaccine or natural exposure to the virus but not necessarily evidence of a protective response. Whole virus mumps-specific antibodies are detected by ELISA in 92-95% of those vaccinated with one dose of the Jeryl Lynn genotype A vaccine and in 95-100% after the second

dose.[3] Protective efficacy of the MMR vaccine is lower than seroconversion demonstrated by ELISA: 78% after one dose and 88% after two doses. There are numerous examples where groups with high anti-mumps titers are susceptible to infection while others with low anti-mumps titers are resistant. For instance, between July 2010 and December 2015, there were 23 large outbreaks (defined as ≥20 cases) in 18 states with 20–485 cases per outbreak.[27] Nine of the 23 outbreaks occurred in populations where 85% or more of the people affected had documentation of 2 doses of MMR vaccine.[27] Thus, the DoD reliance on the presence of antibodies to the mumps virus as a determinant for administering MMR vaccine at BMT may not be justified and requires reconsideration.

SAFETY AND EFFICACY OF A THIRD DOSE OF MMR VACCINE

A third dose of MMR vaccine has at least a short-term benefit for persons in outbreak settings.

Three epidemiologic studies provided evidence of enhanced mumps prevention following administration of a third dose of MMR vaccine. These studies were conducted in outbreak settings among populations, of which a large percentage have received the recommended 2 doses of MMR vaccine (schools and a university).[30-32] All studies reported lower attack rates among persons who received the third dose during the outbreak compared with persons who had only received 2 doses before the outbreak, although only one study found a statistically significant risk reduction (6.7 versus 14.5 per 1,000 person-years; $p<0.001$).[30] Incremental vaccine effectiveness of the third versus the second MMR vaccine dose in these studies ranged from 61% to 88%, with one estimate being statistically significant (78.1% [95% confidence interval 60.9%–87.8%]).[30]

Three other studies evaluated the geometric mean titers of mumps virus–specific antibodies after administration of the third dose of MMR vaccine and demonstrated a significant increase ($p<0.0001$) 1 month after vaccination.[30-32] One year later, antibody titers declined to near baseline in two of the studies; the other study of a third MMR vaccine dose administered in a non-outbreak setting reported a one-year decline to a level above baseline.[33] Since a decline in antibody is not correlated with a decline in protection against mumps infection, the clinical significance of these laboratory findings is unclear.

Following the institution of a routine third dose at the time of enlistment, the Korean Armed Forces reported a 3-year decrease in the incidence of mumps in military personnel from 58.1 to 26.3 cases per 100,000. During this same period of time the civilian population experienced an increase in the incidence of mumps from 6.7 to 29.7 cases per 100,000.[34] This study provides clear evidence of extended protection following administration of a third dose of MMR vaccine at BMT.

Adverse effects specific to a third or more dose of MMR vaccine are less well defined. Post-marketing studies and the Vaccine Adverse Event Reporting System (VAERS) do not have enough specificity to link adverse effects to the ordinal number of doses, and the majority of adverse effects related to third doses come from studies of its use in outbreaks. With a third dose of MMR vaccine, young adults immunized during an outbreak in Iowa had the following adverse effects at low frequencies: lymphadenopathy, diarrhea, headache, and joint pain.[35] These adverse events occurred within 28 days of the dose and lasted fewer than three days. After receipt of a third MMR vaccine dose for outbreaks in New York (2009-10) and Guam (2010), 6-7.2% had at least one local or systemic reaction within two weeks, with the most common being injection site reactions and joint or muscle aches; there were no serious adverse effects reported with a third MMR vaccine dose in either outbreak.[31,32] In New York, a pre-adolescent was diagnosed with asymptomatic thrombocytopenia one month after receipt of a third dose of MMR vaccine during the 2010 outbreak; record review revealed mild thrombocytopenia on laboratory tests performed 4 years prior.[36] A Dutch study of 150 young adults who received a third non-outbreak dose of MMR vaccine reported no serious adverse effects with only transient mild effects lasting less than 4 weeks.[33] In general, adverse effects rates reported with the use of a third dose of MMR vaccine are similar to those reported after a 1st or 2nd dose.[36] The more serious adverse events reported following administration of MMR vaccine — allergic reactions including anaphylaxis, encephalitis, seizures, and thrombocytopenia — are associated with the measles component of the MMR vaccine.[37] The rubella component of MMR vaccines, in adults, may be associated with acute joint symptoms, transient

arthralgia, or arthritis.[38] Reactions to the mumps component are primarily mild. Some mumps vaccines strains have been associated with aseptic meningitis. This has not been demonstrated for the Jeryl Lynn strain found in the current MMR vaccine.[37] These findings support the development of a monovalent mumps vaccine of genotype G to match the mumps strain prevalent in the U.S..

The DoD should continue to follow CDC guidelines for contraindications for individuals with a contraindication for use of the MMR vaccine (M-M-R® II): those who have had a severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component; have a known severe immunodeficiency (e.g., from hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, or long-term immunosuppressive therapy or patients with human immunodeficiency virus infection who are severely immunocompromised); are pregnant; or have a history of anaphylactic reactions to neomycin.[38]

MILITARY COST CONSIDERATIONS FOR THE MUMPS IMMUNIZATION STRATEGY

The 2010 DHB Report on mumps immunizations and the 2019 MHS Strategy Map both value lower costs in addition to readiness.[1,39] Cost considerations for mumps immunization strategies include cost of the MMR vaccine and of antibody screening tests. The table lists the costs of vaccine and laboratory testing for universal and selective immunization and testing strategies. The cost of the manpower to collect the screening tests and administer the vaccine is more difficult to estimate.

Estimated Annual Vaccine and Laboratory Costs of Immunization and Laboratory Screening Strategies for Protection Against Measles, Mumps, and Rubella in U.S. Military Accessions (in $ millions)

	Vaccines ($m)	Laboratory Test ($m)	Total ($m)
Selective immunization with measles/rubella screening	$ 2.1	$ 16.7	$ 18.8
Selective immunization with measles/rubella/mumps screening	$ 2.6	$ 24.8	$ 27.4
Universal vaccination with no laboratory testing	$ 7.0	$ 0	$ 7.0

Assumptions: 171,000 recruits/year, $41/vaccine, $49/measles IgG, $49/rubella IgG, $55 mumps IgG, 30% receive vaccine under measles/rubella serology testing, 38% receive vaccine with measles/rubella/mumps serology testing (Labcorp; Personal Communication, Merck; Ryan, Briefing to the DHB Public Health Subcommittee, Feb 2020)[2]

Public health researchers have estimated costs to respond to mumps outbreaks in non-military settings. In a University of Iowa outbreak, the estimated costs to address and contain a mumps outbreak with 4,736 MMR vaccine doses (a population roughly equivalent to that of an aircraft carrier) are $649,000 and 6,300 person-hours.[40] Other published estimates include $463,000, roughly 8,000 person-hours, and 1,812 MMR vaccine doses for an outbreak in New York and $257,000, over 8,000 person-hours, and 2,800 MMR vaccine doses for an outbreak in Guam.[41,42]

However, the cost of a military unit unable to perform its mission is even more difficult to determine as it involves current and future geopolitical and economic considerations as well as potential degradation of operational readiness, costs from mission planning, and lost opportunity costs from impacted mission execution. The DHB presumes that the latter uncalculatable costs dwarf the costs of vaccine, laboratory testing, and manpower for any recommendation under consideration.

FINDINGS

1. **Outbreaks of mumps can have a significant impact on military readiness.**

   Despite the current DoD practice of directly or indirectly screening for antibodies to mumps and boosting recruits with low mumps titers, there have been recent outbreaks on board U.S. naval vessels and within ground units of the U.S. military that put both military and civilian personnel at risk, are financially costly, disrupt the mission, and potentially compromise unit readiness.

2. **Two doses of the MMR vaccine reduce the risk of developing mumps infections, but protection is not complete.**

   Despite relatively high mumps vaccine rates, there have been recent large-scale outbreaks of mumps in the U.S.

3. **There is no reliable laboratory surrogate of protection against mumps infection. The presence or absence of antibodies against the mumps virus detected with current methodologies is not a reliable indicator of protection or future susceptibility to mumps infection.**

   There is discordance between mumps antibody titers, as determined by enzyme linked immunosorbent assay or plaque reduction neutralization, and protection. There are numerous examples where groups with high anti-mumps titers are susceptible to infection while others with low anti-mumps titers are resistant. The loss of mumps protection is best correlated with time since last immunization. This is reflected by a waning humoral and cellular immune response (the latter not well delineated, which may account in part for the discordance between antibody titers and protection), individual genetic differences in immune responses, and antigenic differences in circulating wild-type virus strain (genotype G) and vaccine virus strain (genotype A).

4. **Administration of a third MMR vaccine dose offers an additional margin of protection against mumps infection. At present, this is only available for those older than 18 years of age through administration of the trivalent MMR vaccine.**

   Epidemiologic studies reported lower attack rates among persons who received the third dose during the outbreak compared with persons who had received 2 doses before the outbreak. Following the institution of a routine third dose at the time of enlistment, the Korean Armed Forces reported a 3-year decrease in the incidence of mumps in military personnel.

RECOMMENDATIONS

1. **Immunization strategy for new recruits:**

   Administer one dose of MMR vaccine to all new recruits regardless of their previously documented immunization history (e.g., immunization records). Administer another dose of MMR vaccine one month later for recruits who had zero or only one documented MMR vaccinations prior to entering the DoD. The DoD should continue to follow CDC guidelines for individuals with a contraindication for use of the MMR vaccine.

2. **Immunization strategy for other Service members who have not received a documented 3 doses:**

   Administer one dose of MMR vaccine to:

   - Service members assigned to bases in host countries with endemic mumps, as determined by the Centers for Disease Control and Prevention
   - Service members assigned to submarines or other units to be deployed for an extended period of time without access to regular communication, without logistical support in the event of a mumps outbreak, or in times of significant conflict

   This does not prescribe or prohibit the use of an outbreak dose should circumstances warrant.

3. **Family member screening to protect Service members overseas**

   Ensure family members older than 4 years of age who are accompanying Service members to countries with endemic mumps have received the CDC recommended 2 doses of MMR vaccine, unless the family member can provide documentation for a medical exemption.

4. **Inclusion of mumps vaccine research as a DoD research priority**

   The DoD should establish intramural or extramural research programs to help develop a monovalent genotype G mumps vaccine or mumps vaccine against all genotypes, identify correlates of protective immunity, and better define the duration of protection.

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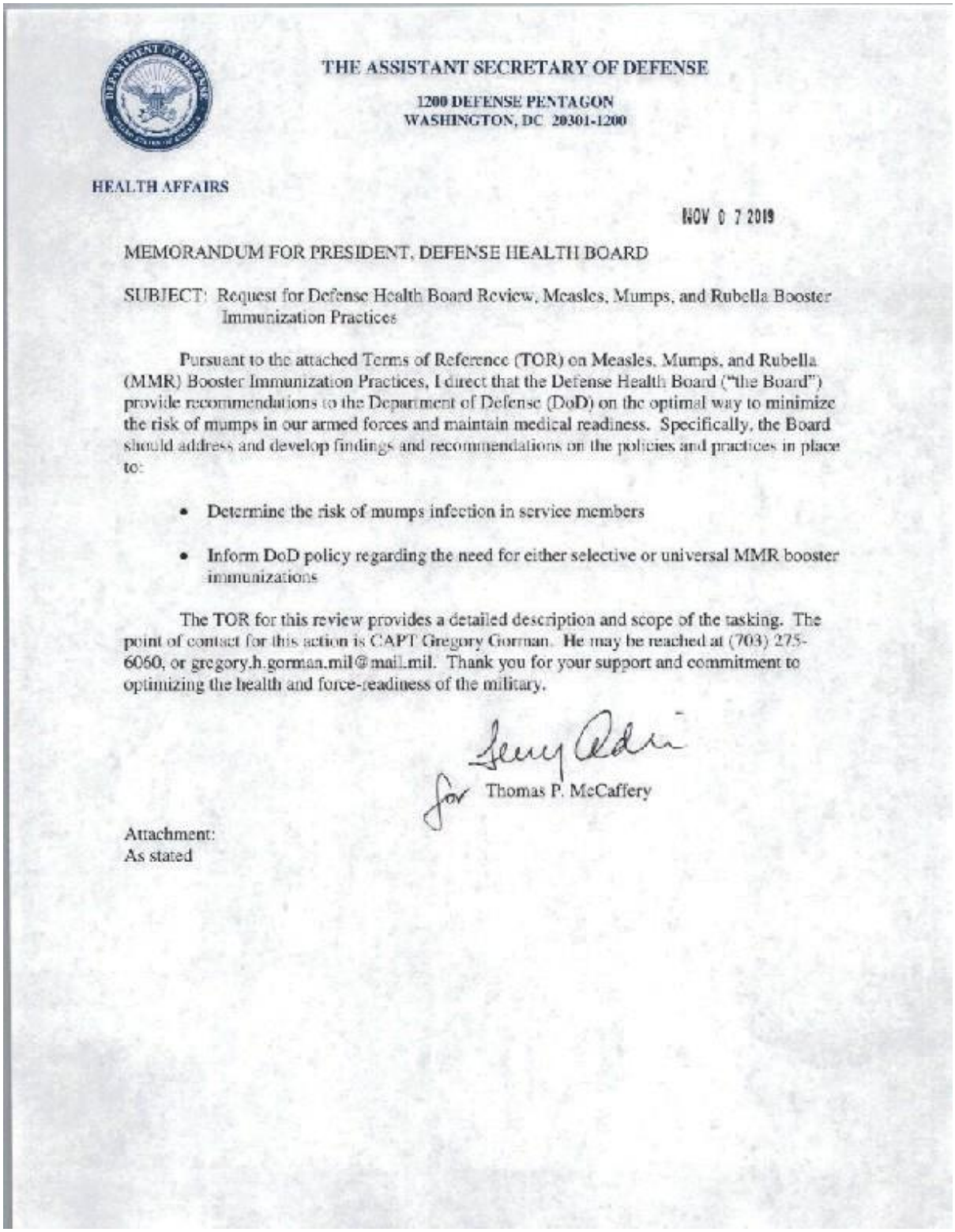
Appendix B: Charge to the Defense Health Board



THE ASSISTANT SECRETARY OF DEFENSE

1200 DEFENSE PENTAGON
WASHINGTON, DC 20301-1200

HEALTH AFFAIRS

NOV 0 7 2019

MEMORANDUM FOR PRESIDENT, DEFENSE HEALTH BOARD

SUBJECT: Request for Defense Health Board Review, Measles, Mumps, and Rubella Booster Immunization Practices

Pursuant to the attached Terms of Reference (TOR) on Measles, Mumps, and Rubella (MMR) Booster Immunization Practices, I direct that the Defense Health Board ("the Board") provide recommendations to the Department of Defense (DoD) on the optimal way to minimize the risk of mumps in our armed forces and maintain medical readiness. Specifically, the Board should address and develop findings and recommendations on the policies and practices in place to:

- Determine the risk of mumps infection in service members
- Inform DoD policy regarding the need for either selective or universal MMR booster immunizations

The TOR for this review provides a detailed description and scope of the tasking. The point of contact for this action is CAPT Gregory Gorman. He may be reached at (703) 275-6060, or gregory.h.gorman.mil@mail.mil. Thank you for your support and commitment to optimizing the health and force-readiness of the military.

for Thomas P. McCaffery

Attachment:
As stated

Defense Health Board
Measles, Mumps, and Rubella Booster Immunization Practices
TERMS OF REFERENCE

These terms of reference (TOR) establish the objectives for the Defense Health Board ("the Board"), through its Public Health Subcommittee, to conduct an independent review of measles, mumps, and rubella (MMR) immunization practices for Service members.

Mission Statement: The mission of the Board is to provide independent advice and recommendations to maximize the safety and quality of, as well as access to, health care for Department of Defense (DoD) health care beneficiaries.

Issue Statement: "Required immunizations [of Service members] will be monitored and kept current" as outlined in the Department of Defense Instruction (DoDI) 6025.19, "Individual Medical Readiness." The DoD follows the Centers of Disease Control and Prevention's (CDC) immunization guidelines for the general US population to ensure Service members have received 2 doses of the MMR vaccine, ideally at 12-15 months and 4-6 years of age.[1] Since the introduction of the two-dose schedule, the incidence of all three diseases decreased. Recently, measles and mumps cases have increased as nation-wide population immunity has decreased, with mumps outbreaks affecting military readiness.[2-5]

At present, recruits are screened for immunity to measles, mumps, and rubella by measuring measles and rubella virus-neutralizing antibody levels. Mumps titers are not measured due to low sensitivity and their poor predictive value of immunity.[6] Measles and rubella titers are used as proxy-measures for mumps immunity. Recruits are given a MMR booster dose if measles or rubella antibody levels are low.[7]

The mumps component of the MMR vaccine has the highest rate of waning immunity among the three components.[6] A quarter of immunized individuals lose mumps immunity within 7-9 years.[2] If the second dose of MMR was given ≥13 years, the risk of mumps is nine times higher than if given <12 years of age.[8] Social and environmental factors also contribute to increased mumps transmission, such as close social contacts and living conditions as seen in military barracks and ships. Therefore, the Advisory Committee on Immunization Practices recommends that:

> *Persons previously vaccinated with 2 doses of a mumps virus-containing vaccines who are identified by public health authorities as being part of a group or population at increased risk for acquiring mumps because of an outbreak should receive a third dose of a mumps virus-containing vaccines to improve protection against mumps disease and related complications.*[9]

In 2010, the Board reviewed this topic and did not recommend a universal third MMR immunization strategy, with the caveat that such a strategy should be instituted in the event of an increased risk of mumps. Since that recommendation, there have been mumps outbreaks in 2019 that have led to the quarantine of USS FORT MCHENRY and re-immunization of paratroopers stationed at Aviano AFB in Italy.

Objectives and Scope: The Board, through its Public Health Subcommittee, will determine if universal administration of MMR vaccine at accessions and a booster vaccine for current service members is warranted in light of recent mumps outbreaks and effects on readiness. Specifically, the Board's Public Health Subcommittee should:

- Review scientific literature and epidemiologic trends to quantify current and future risk to medical readiness from mumps outbreaks.
- Determine if current immunization policy is sufficient to mitigate potential risk and, if not, recommend best practices to mitigate that risk.
- Provide any additional recommendations to inform policy, such as impact to budgetary and logistical requirements.

Methodology:

1. The Public Health Subcommittee assessment will be conducted in compliance with the Federal Advisory Committee Act, DoDI 5105.04, "Department of Defense Federal Advisory Committee Management Program," the General Services Administration's Federal Advisory Committee Management; Final Rule, and the Board's Charter.
2. The Public Health Subcommittee should focus on improving immunization policies that enhance medical readiness.
3. The Public Health Subcommittee may seek input from other sources with pertinent knowledge or experience.

Deliverables:

The Public Health Subcommittee will complete its work within six months of receiving the tasking and report to the Board in a public forum for a full and thorough deliberation. The Board will, in accordance with its Charter, report to the Assistant Secretary of Defense for Health Affairs, who has been delegated the authority to evaluate the independent advice and recommendations received from the Board and, in consultation with the Under Secretary of Defense for Personnel and Readiness, identify actions or policy adjustments to be made by DoD in response. The Public Health Subcommittee will provide progress updates at each Board meeting while working the tasking.

Required Support:

1. The Defense Health Board Support Division will provide any necessary research, analytical, administrative, and logistical support for the Board and the Public Health Subcommittee.
2. Funding for this review is included in the division's operating budget.
3. In accordance with the November 26, 2018 Deputy Secretary of Defense memo, "Advisory Committee Management," and DoDI 5105.04, "the Board and the Public Health Subcommittee shall receive full and timely cooperation of each office of the Secretary of Defense and DoD Component Head in providing analyses, briefings, and other DoD information or data necessary for the fulfillment of its responsibilities as provided for by this TOR and in conformance with applicable security classifications.

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Appendix C: Methods

Directed by the TOR and based on current mumps outbreaks within military populations, the DHB Support Division team performed a comprehensive search and review of mumps infection. First, the search focused on scientific, peer-reviewed public health and military-specific research articles on mumps surveillance and outbreak case studies. However, to fully understand the scope of mumps infection, the DHB Support Division team also reviewed scientific systematic reviews and military and civilian immunization policies on mumps. The team identified the initial pool of subject experts from published work relevant to the TOR's tasking and objectives. These experts from infectious disease, preventive medicine, and public health (from academia, private industry, government, and the military) briefed to the Subcommittee on the virology, epidemiology, laboratory testing, military relevance, and preventive measures related to mumps infection. During these briefings, the Subcommittee members engaged with the experts asking clarifying questions to better understand mumps disease impact on populations and revisiting the objectives of the TOR's tasking. Through multiple meetings and iterative review of scientific literature, subject matter expert briefings, and key discussions the Subcommittee members discussed the current state of mumps vaccine science, the epidemiology of mumps infection, the impact an outbreak has on military readiness, and identified existing and best practices for mumps infection prevention. From these Subcommittee discussions, the DHB Support Division team used data condensation methods (e.g., categorizing, theming, indexing) to provide background for the Subcommittee to draft its findings and recommendations. The Subcommittee Chair briefed the findings and recommendations to the DHB in an open forum, with discussion by DHB members and opportunity for input by the public.

Appendix D: Meetings and Presentations

February 10, 2020: Defense Health Board Meeting
Falls Church, VA

Dr. H. Clifford Lane provided an introduction and overview of the tasking to the DHB Members.

February 25-26, 2020: Public Health Subcommittee Meeting
Falls Church, VA

The Subcommittee met in-person and received briefings from military and civilian SMEs on mumps virology and epidemiology, Service representatives who responded to the current mumps outbreaks, and DHA policy makers.

The SMEs who briefed at the meeting:

- CDR Shawn Clausen, Armed Forces Health Surveillance Branch, DHA
- LCDR Matthew Hall, Navy Marine Corps Public Health, Bureau of Medicine and Surgery
- Dr. Carole Hickman, National Center for Immunizations & Respiratory Diseases, CDC
- Dr. Mona Marin, National Center for Immunizations & Respiratory Diseases, CDC
- Dr. Mariel Marlow, National Center for Immunizations & Respiratory Diseases, CDC
- CDR Manisha Patel, National Center for Immunizations & Respiratory Diseases, CDC
- Dr. Gregory Poland, Mayo Vaccine Research Group, Mayo Clinic
- Dr. Paul Rota, National Center for Immunizations & Respiratory Diseases, CDC
- Dr. Shauna Stahlman, Armed Forces Health Surveillance Branch, DHA
- Col Tonya Rans, Immunization Healthcare Branch, DHA
- Dr. Margaret Ryan, Immunization Healthcare Branch, DHA

March 17, 2020: Public Health Subcommittee Video Teleconference

The Subcommittee met virtually and received briefings from military and civilian SMEs on mumps vaccine development, use, and safety. The members also discussed sections of the report.

The SMEs who briefed at the meeting:

- Dr. Judy Beeler, Center for Biologics Evaluation and Research, FDA
- CAPT Ann Schwartz, Center for Biologics Evaluation and Research, FDA

March 31, 2020: Public Health Subcommittee Video Teleconference

The Subcommittee met virtually and discussed sections of the report. There were no briefings at this meeting.

April 14, 2020: Public Health Subcommittee Video Teleconference

The Subcommittee met virtually and discussed the report. There were no briefings at this meeting.

April 21, 2020: Public Health Subcommittee Video Teleconference

The Subcommittee met virtually and discussed the report. There were no briefings at this meeting.

April 28, 2020: Public Health Subcommittee Video Teleconference

The Subcommittee met virtually and discussed the report. There were no briefings at this meeting.

May 5, 2020: Public Health Subcommittee Video Teleconference

The Subcommittee met virtually and discussed the report. There were no briefings at this meeting.

May 18, 2020: Defense Health Board Video Teleconference

The Subcommittee Chair provided a decision brief to DHB members. The DHB members voted to approve the report and its findings and recommendations.

Appendix E: Glossary

AIT	Advanced Individual Training
ASD(HA)	Assistant Secretary of Defense for Health Affairs
ASIP	Accessions Screening and Immunization Program
BMT	Basic Military Training
CDC	Centers for Disease Control and Prevention
DHB	Defense Health Board
DoD	Department of Defense
ELISA	Enzyme Linked Immunosorbent Assay
IgM	Immunoglobulin M
MMR	Measles, Mumps, Rubella
M-M-R® II	Measles, Mumps, Rubella Virus Vaccine Live
PRN	Plaque Reduction Neutralization
R_0	R-naught
RNA	Ribonucleic Acid
rRT-PCR	Real-Time Reverse-Transcription Polymerase Chain Reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SME	Subject Matter Expert
Tdap	Tetanus, Diptheria, Pertussis
U.S.	United States
VAERS	Vaccine Adverse Event Reporting System


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