



Notice to reader: The errors in the references have been corrected

An Advisory Committee Statement (ACS)

National Advisory Committee on Immunization (NACI)

Use of Measles-Mumps-Rubella (MMR) Vaccine
for the Management of Mumps Outbreaks in
Canada

PROTECTING AND EMPOWERING CANADIANS TO IMPROVE THEIR HEALTH



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Revised publication: 2024

Cat.: HP40-286/2024E-PDF

ISBN: 978-0-660-71723-4

Pub.: 240116

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Original publication: July 2021

Cat.: HP40-286/2021E-PDF

ISBN: 978-0-660-38433-7

Pub.: 240116

Preamble

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (PHAC) with ongoing and timely medical, scientific, and public health advice relating to immunization.

In addition to burden of disease and vaccine characteristics, PHAC has expanded the mandate of NACI to include the systematic consideration of programmatic factors in developing evidence-based recommendations to facilitate timely decision-making for publicly funded vaccine programs at provincial and territorial levels.

The additional factors to be systematically considered by NACI include: economics, ethics, equity, feasibility, and acceptability. Over the coming years NACI will be refining methodological approaches to include these factors. Not all NACI Statements will require in-depth analyses of all programmatic factors. As NACI works towards full implementation of the expanded mandate, select Statements will include varying degrees of programmatic analyses for public health programs.

PHAC acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and is disseminating this document for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph(s). Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) of the Canadian manufacturer(s) of the vaccine(s). Manufacturer(s) have sought approval of the vaccine(s) and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of PHAC's policy on conflict of interest, including yearly declaration of potential conflict of interest.

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SUMMARY OF INFORMATION CONTAINED IN THIS NACI STATEMENT

The following highlights key information for immunization providers. Please refer to the remainder of the Statement for details.

1. What

Mumps

Since 2016, there has been a substantial increase in the number of reported mumps outbreaks and outbreak-associated mumps cases in Canada. The majority of outbreak-related mumps cases in Canada in recent years have occurred in young adults aged 15-39 years. Geographically, outbreaks in northern Canadian communities have had higher attack rates. In addition, outbreaks among vaccinated individuals often occur in situations with increased risks for exposure to the virus and transmission may be facilitated through behavioural risk factors.

Complications such as orchitis and oophoritis are relatively frequent; permanent sequelae like deafness are rare. While complications of mumps infections are not always well characterized or reported, they are less common in the post-vaccine era and among those vaccinated.

Additional information about Mumps is available on the Government of Canada web site (<https://www.canada.ca/en/public-health/services/immunization/vaccine-preventable-diseases/>).

Vaccine

Mumps vaccine is available as measles-mumps-rubella (MMR) or measles-mumps-rubella-varicella (MMRV) vaccine. Mumps vaccine effectiveness has been estimated at 62% to 91% for 1 dose and 76% to 95% for 2 doses. Somewhat lower vaccine effectiveness has been observed in outbreak settings, especially when exposures occurred in close-contact settings as protection appears to wane over time. Waning vaccine effectiveness is likely due to decline in cellular immunity, antibody concentrations and avidity.

Reactions to mumps vaccine are generally mild and transient and include pain and redness at the injection site, fever, and rash.

2. Who

This Statement provides an evidence summary and recommendations on the topic of additional dose(s) of MMR vaccine provided in mumps outbreak settings, including the off-label administration of a third dose of MMR vaccine (MMR3) in individuals who were previously vaccinated with two valid doses, for consideration by public health programs.

3. How

In an outbreak setting, NACI recommends that implementation of an outbreak dose of MMR vaccine may be considered as a part of the broader outbreak management strategy. In addition, NACI recommends that MMR vaccine (up to a third dose) may be considered for close contacts following exposure to a case of mumps in an outbreak setting. However, due to the potential logistical challenges that are associated with program implementation (such as those related to vaccine supply and acquisition costs, vaccine uptake and virus susceptibility determination and the

absence of immunization records or information on the exposures), it is important to promptly assess the outbreak characteristics and define the populations that have or may be exposed to the disease.

4. Why

Mumps occurs worldwide and outbreaks continue to occur. Complications of mumps disease are relatively frequent, although permanent sequelae are rare.

I. INTRODUCTION

I.1 Objective of this Statement

In 2018, following a period of elevated mumps activity in Canada, Canadian provinces and territories signalled interest in a review of evidence on the use of additional doses of mumps-containing vaccine in outbreak settings. The United States Advisory Committee on Immunization Practices (ACIP) has recommended the use of a third dose of a mumps-containing vaccine during mumps outbreaks to improve protection against mumps disease and related complications ⁽¹⁾. The primary objective of this statement is to review the evidence on the effectiveness and safety of additional dose(s) of MMR vaccine when provided in mumps outbreak settings, including the off-label administration of a third dose of MMR vaccine (MMR3) in individuals who were previously vaccinated with two valid doses. A literature and environmental evidence review was undertaken to develop recommendations for the use of additional dose(s) of MMR vaccine in mumps outbreak settings. In developing this guidance, NACI reviewed evidence relating to:

- Programmatic recommendations with consideration given to the number and timing of additional MMR vaccine dose(s) with the following objectives:
 - Primary: To control the scale of mumps outbreaks in Canada by limiting the number of cases; and
 - Secondary: To prevent complications from mumps (e.g., orchitis, oophoritis, meningitis, encephalitis, hearing loss).
- Individual recommendations with consideration given to the number and timing of additional doses in outbreak settings for the protection of individuals who are not covered by programmatic recommendations.

The vaccine recommendations and other information provided in this Statement are intended to complement and, where applicable, update the Guidelines for the Prevention and Control of Mumps Outbreaks in Canada published in 2010, which provide more detailed and comprehensive information on the principles of mumps outbreak management beyond immunization.

I.2 Background on Mumps Immunization Programs and Recommendations in Canada

The recently updated national disease reduction target for mumps is to maintain less than 100 annual cases ⁽²⁾, based on a 5-year rolling average. However, given the observed waning of mumps immunity following the administration of two doses of MMR vaccine ⁽³⁻⁸⁾, there is acknowledgment that this target may be difficult to achieve currently with routine schedule.

Immunization with MMR vaccine has been demonstrated to effectively prevent mumps, viral transmission and disease complications ⁽⁹⁾. For routine immunization of children, since 1996, NACI has recommended the administration of 2 doses of mumps-containing vaccine after a child's first birthday. The first dose of mumps-containing vaccine [MMR or Measles, Mumps, Rubella and Varicella (MMRV) vaccine] should be provided at 12 to 15 months of age and the second dose at 18 months of age or any time thereafter, but no later than school entry.

The current national immunization target is to achieve 95% vaccination coverage for receipt of two doses of mumps-containing vaccine by seven years of age ⁽²⁾.

Recommendations for adults vary from 0 to 2 doses, depending on the individual's age and risk of exposure. Two doses of measles-containing vaccine (which also includes mumps) are recommended for those who are at the greatest risk of mumps exposure (travellers to destinations outside of Canada, students in post-secondary educational settings born after 1970, and all health care workers and military personnel) ⁽¹⁰⁾. In outbreak settings, NACI recommends that an additional dose of mumps-containing vaccine be provided to adults born in or after 1970 who have not already received two doses of the MMR vaccine ⁽¹¹⁾. Adults born before 1970 are generally presumed to have acquired natural immunity to mumps; however, some of these individuals may be susceptible ⁽¹²⁾.

While the exact cause of mumps outbreaks in highly vaccinated populations remains unknown, several factors have been proposed as possible contributors to breakthrough infections ^(3, 4, 7, 13-19):

- Waning of immunity following vaccination ^(3, 5-8, 20); studies have shown differential humoral immunity for each of measles, mumps, and rubella, even though they are combined in the MMR vaccine. Mumps antibody levels have consistently shown to be lower compared to measles and rubella ⁽²¹⁾;
- Reduced vaccine effectiveness due to antigenic differences between circulating and vaccine virus strains ^(3, 22-24);
- High intensity of exposure to the virus in close-contact settings, coupled with behaviours that increase the risk of transmission ^(3, 22-26);

II. METHODS

II.1 Burden of Illness

In brief, the broad stages in the preparation of a NACI advisory committee statement are:

1. Knowledge synthesis;
2. Synthesis of the body of evidence of benefits and harms, considering the quality of the evidence and magnitude of effects observed; and
3. Translation of evidence into a recommendation.

Details regarding NACI's evidence-based process for developing a Statement are outlined in [Evidence-based Recommendations for Immunization – Methods of the National Advisory Committee on Immunization](#).

NACI reviewed the key questions for the literature review as proposed by the NACI MMRV Working Group (MMRV WG), including such considerations as the burden of illness and the target population(s); the safety and effectiveness of the vaccine; vaccine schedules; and other aspects of the overall immunization strategy. NACI also reviewed the national surveillance data for mumps which is routinely reported to the Public Health Agency of Canada (PHAC) by provincial and territorial departments of health through the Canadian Notifiable Disease Surveillance System (CNDSS) ⁽²⁷⁾. To complement these data, the provinces and territories were surveyed for information on mumps outbreaks occurring from January 2016 to August 2018.

The literature review and knowledge synthesis were performed by PHAC staff and supervised by the NACI MMRVWG. Following critical appraisal of individual studies, proposed recommendations for vaccine use were developed. The evidence and proposed recommendations were presented to NACI for deliberation on September 25, 2019 and February 6, 2020. NACI approved the recommendations on November 18, 2020, following thorough review of the evidence to assess the risk-benefit of the use of mumps-containing vaccine in outbreak settings. The description of relevant considerations, rationale for specific decisions, and knowledge gaps are described in the text.

II.2 NACI Literature Review (Effectiveness and Safety)

The policy questions addressed in this statement are:

Should an additional dose of mumps-containing vaccine be provided in an outbreak setting? If so, who should receive it?

The literature search and data extraction conducted on January 2, 2019 used the following population, intervention, comparator and outcomes (PICO 1):

Population:	Persons, all ages, at risk of mumps infection due to outbreaks receiving an outbreak dose of MMR vaccine
Intervention:	Provision of MMR vaccine during a mumps outbreak
Comparator:	Persons, all ages, at risk of mumps infection due to an outbreak with documented MMR vaccination status who did not receive a dose of MMR vaccine during the outbreak Persons, all ages, at risk of mumps infection due to an outbreak with documented MMR vaccination status who did not receive an outbreak dose
Outcomes:	Effectiveness and safety of MMR3

The supplementary literature search and data extraction conducted on July 16, 2019 used the following PICO 2:

Population:	Persons, all ages, receiving a dose of MMR vaccine within 7 days of exposure to mumps
Intervention:	Post exposure dose of MMR vaccine
Comparator:	Persons, all ages, who did not receive a post-exposure dose of MMR
Outcomes:	Effectiveness of a post-exposure dose of MMR

MEDLINE and EMBASE electronic databases were searched using search terms and strategies developed with the assistance of a Health Canada library specialist. The results of a systematic review conducted by the US Centre for Disease Control and Prevention (CDC) supporting the ACIP, assessing the use of a third dose of a mumps containing vaccine (MMR3) in outbreak settings, were also reviewed and used as a foundation for the NACI systematic review. NACI modified the CDC literature review strategy in order to integrate additional studies on “outbreak dose” of MMR vaccine, defined as an additional dose (defined as a catch-up dose which could include a third dose) provided in an outbreak setting. In order to fully align with the NACI MMRV Working Group PICO 1, studies published between January 2000 and January 2, 2019 were retrieved and screened by title, abstract and full-text for potential eligibility by two reviewers. The same reviewers also conducted the additional data screening extraction for the NACI MMRV Working Group PICO 2, which was requested by the WG in order to determine the effectiveness of a mumps-containing vaccine when used post-exposure. PICO 2 included studies that were published between 1946 and July 16, 2019. Hand-searching of the reference lists of included articles was performed by one reviewer to identify additional relevant publications. One reviewer extracted data from the studies included for review into an evidence table using a piloted data abstraction template designed to capture information on study design, population and outcomes of interest. A second reviewer independently validated the abstracted data with any disagreements or discrepancies resolved by discussion and consensus. The level of evidence (i.e., study design) and methodological quality of included studies was assessed independently by the two reviewers using the design-specific criteria by Harris et al. (2001) ⁽²⁸⁾ adopted by NACI for rating the internal validity of individual studies (Tables 1, 2).

III. EPIDEMIOLOGY

III.1 Disease Characteristics and Burden of Illness

Mumps virus, the causative agent of mumps infection, is an enveloped RNA virus that belongs to the genus Rubulavirus in the family Paramyxoviridae ⁽²⁹⁾. Infection is spread through large droplet transmission over short distances of less than two meters or by direct contact with infected respiratory droplets or saliva, and symptoms occur after an incubation period between 12 and 25 days (average 16 to 18 days). Typically, mumps is a relatively mild disease with parotitis being the most frequently observed clinical manifestation. However, subclinical and asymptomatic infections are common ⁽²⁹⁻³²⁾. In rare cases, mumps infection may have permanent sequelae: meningoencephalitis can result in paralysis, seizures, cranial nerve palsies, hydrocephalus and deafness, while orchitis and oophoritis can result in sterility ⁽³³⁻³⁵⁾. Infection during the first trimester of pregnancy has not been associated with congenital anomalies ⁽³⁶⁾, but may increase the rate of spontaneous abortion. The risk and the severity of complications, such as orchitis, oophoritis, meningitis, encephalitis, hearing loss and pancreatitis, may be reduced in partially or fully immunized individuals ^(9, 10, 37-43). Complications are known to occur more frequently among post-pubertal youth and adults than children ⁽⁴⁴⁾.

Although the mumps virus has been isolated from the saliva of persons infected with mumps 7 days before symptom onset to 9 days after, persons infected with mumps are considered most infectious between 2 days before to 5 days after symptom onset. Infected individuals who are asymptomatic can still transmit mumps to others ⁽⁴⁵⁾.

During the pre-vaccine period, mumps was an endemic disease that primarily affected children 5 to 9 years of age. Following the authorization of the mumps vaccine in Canada in 1969 and the subsequent introduction of a routine two-dose MMR vaccination (MMR2) schedule in 1996/97, the number of reported mumps cases nationally decreased by more than 99% ⁽⁴⁵⁾. However, mumps

continues to be a cyclical disease in Canada, with outbreaks occurring every few years and otherwise low incidence rates ⁽⁴⁴⁾. The cohort of individuals born between 1970 and 1990 represents a cohort vulnerable to mumps infection, as these individuals are less likely to have received two doses of mumps-containing vaccine or been alive when the wild virus circulated widely.

In the post-vaccine era, complications from mumps infections are rarely reported. An analysis of Canadian hospitalization data (excluding Quebec) from the Canadian Institute for Health Information (CIHI) was conducted for the calendar years 2014-2018. The number of hospitalizations with a primary diagnosis of mumps (ICD-10-CA code B26 including B26.0, B26.1, B26.2, B26.3, B26.8 and B26.9) was low, with <260 hospitalizations in the 5-year period. Almost half (42%) of the mumps-related hospitalizations were among individuals born before 1970. The number of mumps hospitalizations with severe mumps complications (meningitis and pancreatitis) was extremely low, at two and one cases, respectively, over the 5-year period with all 3 hospitalizations from the cohort born after 1990. Only seven hospitalizations for mumps-related orchitis were identified, with 6/7 hospitalizations from the cohort born after 1990. No information on vaccination status or previous immunity from wild mumps virus infection was available. Although these data support the literature in that severe mumps complications are rare, caution is needed when interpreting these data as this extraction was not validated; the data are not national; and only the hospitalizations with a primary code of mumps were extracted. Co-morbidities and outcomes were not assessed. Age-specific hospitalization data for mumps are not reflective of surveillance data and outbreak data, and this discrepancy should be explored further to better understand the data.

III.2 Mumps Vaccination Coverage

The national vaccination coverage goals aim for 95% of children to have received one dose of measles, mumps and rubella containing vaccine by the age of two years, and 95% vaccination coverage with the recommended two doses of mumps-containing vaccine by seven years of age ⁽²⁾.

Immunization coverage with two doses of mumps containing vaccine varies across Canada's provinces and territories and comprehensive regional coverage data is not currently available. Information on national immunization coverage for mumps and other childhood vaccines in Canada is collected through the Childhood National Immunization Coverage Survey (CNICS). According to the 2017 CNICS, 90% of Canadian children received one dose of MMR vaccine by age two years, and 86% received two doses by age seven years.

In most instances, in Canada, adults born before 1970 are presumed to have acquired natural immunity to mumps. It is important to note that population-level immunity against mumps is not homogenous though, due in part to differences in jurisdictional vaccination strategies over time:

(1) Routine one-dose vaccination against mumps was implemented across provinces and territories between 1970 and 1983, with second dose programs implemented between 1996 and 2001. Overall, individuals born between 1970 and 1996 may only have received one dose or no doses of mumps containing vaccine, and this age cohort may be broader, depending on the province or territory ⁽¹¹⁾. Exceptions to this would be adults identified to be in high risk groups who may have received two lifetime doses of mumps containing vaccines.

(2) Vaccination has been a common strategy to improve mumps immunity in those who were born in 1970 or later if they are deemed to be at higher risk of mumps or measles and so this

would include travellers, health care workers, military personnel and students in post-secondary educational settings.

Additionally, immigrants and other newcomers to Canada may be a susceptible/under-immunized group because they may have received only one dose or no dose of mumps-containing vaccine, given that MMR vaccination is not universal ⁽⁴⁶⁾.

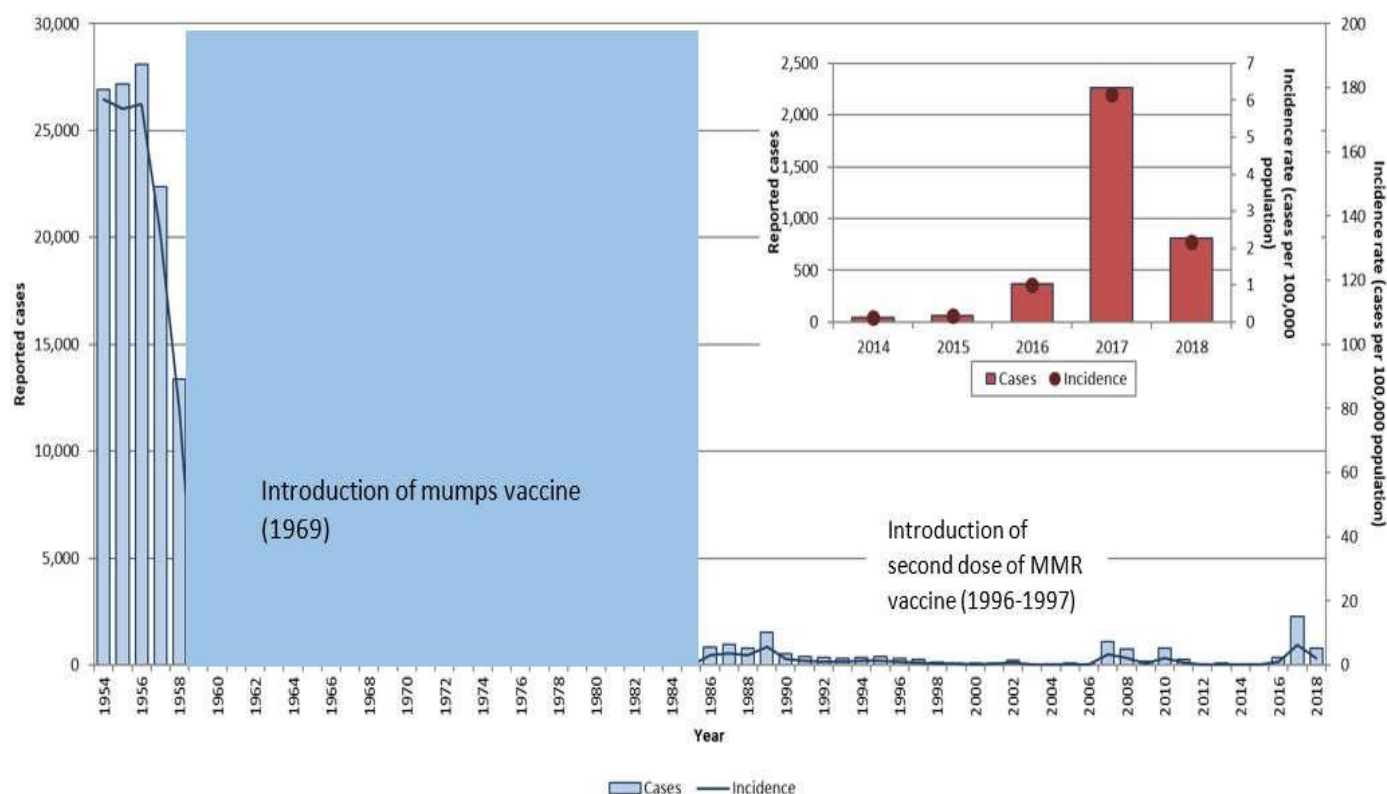
III.3 Description of Mumps Epidemiology in Canada Between 2014 and 2018

Mumps has been a nationally reportable disease since 1986 ^(47, 48) and is currently endemic in Canada, with cyclical outbreaks occurring every two to five years ⁽⁴⁹⁾. Detailed information regarding the case definition and case classification can be found in the Canada Communicable Disease Report (CCDR) section pertaining to mumps. Briefly, the current national definition for a confirmed mumps case requires clinical illness and laboratory confirmation of infection in the absence of recent immunization with mumps-containing vaccine; or a mumps compatible clinical illness in a person with an epidemiological link to a laboratory-confirmed case. A probable case is defined as mumps compatible clinical illness in the absence of appropriate laboratory tests or in the absence of an epidemiological link to a laboratory-confirmed case.

The national surveillance data for mumps have numerous limitations, including timeliness, and limited availability of information on cases regarding vaccination status, disease severity, long-term sequelae, and complications. Data on outbreaks in Canada are not routinely collected through national surveillance. Additionally, the lack of a national immunization registry or immunization registries for all provinces and territories hinders the ability to determine vaccination status of individuals or populations.

With the introduction of current mumps vaccination schedules, the incidence rate of mumps declined from 251.2 cases per 100,000 population during the pre-vaccine era (i.e., prior to 1969) to 1.9 cases per 100,000 population from 2014-2018 (Figure 1) ⁽⁴⁹⁾.

Figure 1: Number and incidence rate (per 100,000 population) of reported mumps cases^a in Canada by year, 1950 to 2018, before and after introduction of mumps-containing vaccine.



From 2014 to 2018, a total of 3,535 cases of mumps were reported nationally. However, 64% of the cases occurred in 2017 and were likely a result of various outbreaks that started in late 2016 and continued into 2017. This resulted in a five-year median of 73 cases per year (range: 40-2,263 cases). The overall incidence for this period was 1.9 cases per 100,000 population, ranging from 0.1 to 6.2 cases per 100,000 (Figure 1). Adults aged 20 to 39 years old accounted for 53% of all mumps cases, with the highest incidence rates among the 20 to 24-year-old age group (3.8 cases per 100,000 population).

In 2017, a total of 2,263 cases were reported in Canada, with a corresponding incidence rate of 6.2 cases per 100,000 population. Although cases were observed in all age groups, incidence rates were highest in the adolescent and young adult population (between 15 and 29 years of age). Fifty-three percent of the cases were male and 90% of the cases were reported in Manitoba, Ontario and British-Columbia.

III.4 Outbreaks in Canada

Outbreaks between 1996 and 2010 have been described in previously-published mumps outbreak guidelines⁽¹¹⁾. Since 2016, there has been a substantial increase in the number and size of mumps outbreaks. In 2017 and in 2018, the provinces and territories were surveyed to collect enhanced

^a Mumps was removed from the list of national notifiable diseases for the years 1959 to 1985

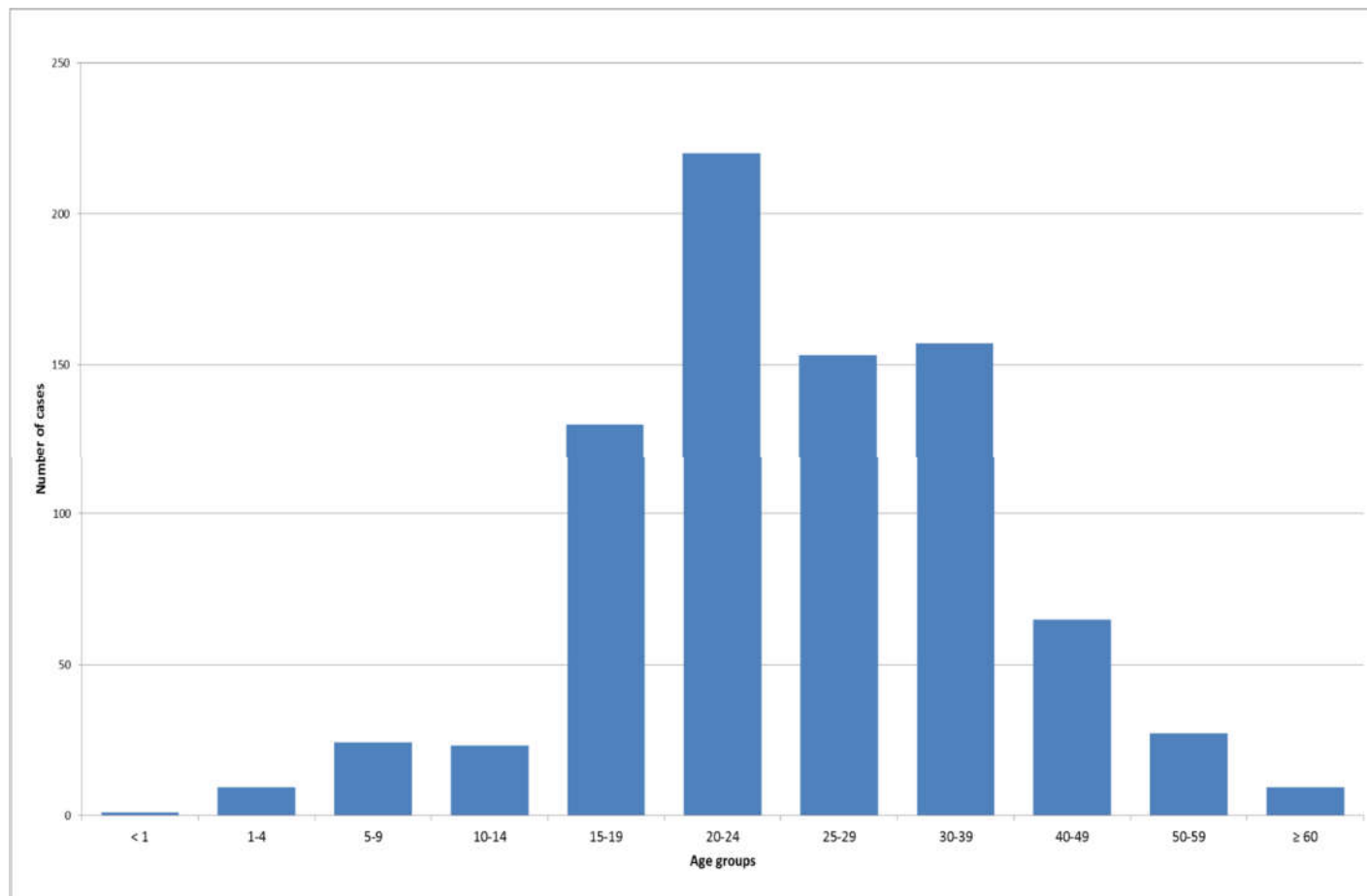
provincial and territorial data on recent mumps outbreaks occurring from January 2016 to February 2017 and from January 2017 to August 2018, respectively ⁽⁵⁰⁾. The purpose of the survey was to provide an overview of mumps activity including public health actions across Canada. This survey was conducted for information sharing among provinces and territories and internally. At that time, provinces and territories were asked to report on outbreak related cases only. No standard definition for an outbreak was used. Information on mumps hospitalisations and complications has not been collected and is not available.

Combined 2017 and 2018 Mumps Outbreak Surveys Results

Using combined data from both surveys from the Provinces and Territories, from January 2016 to August 2018, a total of 881 cases was reported, excluding the Manitoba outbreak (see below), corresponding to 24 outbreaks ⁽⁵⁰⁾. The median outbreak size was 12.5 cases, ranging from 2 to 166 cases. Overall, the mean outbreak duration was 16.5 weeks, ranging from 1 week to 59 weeks. Mumps outbreak activity was reported in at least one jurisdiction from February 2016 to July 2018. Most outbreaks were reported during the first quarter of 2017, with nine outbreaks starting in four provinces and two ongoing outbreaks in two other jurisdictions.

Of the cases for which age information was available (n=814), 80.6% of the outbreak-related cases were between 15-39 years of age, with 25% of the cases occurring among the 20 to 24-year-old age group (n=217 cases) (Figure 2).

Figure 2: Outbreak mumps case counts by age group, from January 2016 to August 2018, in Canada (n=814)



Note: Does not include cases from two outbreaks in Saskatchewan (n=63) for which specific age information were not given

Source: Vaccine Preventable Diseases, Surveillance and Epidemiology Division (SED), Center for Immunization and Respiratory Infectious Diseases (CIRID), Public Health Agency of Canada

The most commonly reported exposure settings included community settings (30.8%), social gatherings (26.9%), post-secondary institutions (19.2%), and sports teams (19.2%). Other exposure settings that were reported (26.9%) include workplace locations, working or living in close quarters, household, and post-secondary settings. Overall, 9 outbreaks (37.5%) were travel related.

Among the cases for which sex information was available (n=816), the majority of cases were male (59%), which is consistent with the sex distribution in the national notifiable disease surveillance system. This is likely due to diagnostic bias as orchitis may be diagnosed more often than oophoritis. It might also be due to differential immunization of females, as they are more frequently screened for rubella and, if susceptible, vaccinated with a mumps-containing vaccine.

Of the outbreak-related cases with known immunization status (n=628), approximately half of cases had received two doses of mumps containing vaccine (49%), 30% had received 1 dose, and 20% were unvaccinated. The remainder (1%) had received 3 doses.

Although the enhanced provincial and territorial surveillance data provides valuable insight on the magnitude and context of recent mumps outbreak activity in Canada, there are several limitations and other relevant factors that should be carefully considered when interpreting these data. First,

there is no standard national outbreak case definition and the categorization of cases as outbreak-related is left to the discretion of each jurisdiction. Additionally, the expected incidence of mumps in Canada has changed significantly over the years, which presents a challenge in establishing a common provincial and territorial threshold for an outbreak definition. Furthermore, challenges with associating cases to unique mumps outbreaks is difficult, especially when a higher than expected number of cases is observed in a community. At the time of the original 2017 provincial and territorial data request, there were no specified end-dates for the ongoing 2016 mumps outbreaks. Therefore, these outbreaks could have continued into 2017, leading to reporting of duplicate case counts. In addition, because only aggregate data were provided, more detailed and in-depth analyses of survey results could not be conducted, including determination of the interval between the last MMR dose and disease onset, the geographical distribution of cases and occurrence of mumps-related complications.

Manitoba Mumps Outbreak 2016-2018

Manitoba reported a major mumps outbreak starting in September 2016. Provincial public health officials conducted a survival analysis to assess the protection of vaccine-induced immunity from infection of mumps from September 2016 to September 2018 ⁽⁵¹⁾. Among northern residents during this study period, vaccine-induced immunity waned over time, and the impact of vaccination with 1 dose and with 2 doses on waning was assessed. By end of the provincial outbreak, 2,223 cases were counted, 51.7% of whom were male. The overall cumulative incidence was 1.6 cases per 1,000 population. The median age was 25 years and the highest incidence rate was among the 18 to 29-year-old age group (3.4 cases per 1,000). Although 70.4% (n=1,566) of all cases were from the northern region, the most rural region of Manitoba with a large number of isolated communities, the outbreak originated in the Winnipeg Regional Health Authority. The outbreak spread from the affected urban center to rural areas across the province. The two-dose coverage of mumps containing vaccine was about 70% in confirmed cases who had records in the provincial registry. Among cases vaccinated with at least two documented doses of mumps-containing vaccine, a median of 11 years had passed since individuals received their most recent dose, suggesting waning of vaccine-induced immunity against mumps. Analysis of cases from the northern region indicated that the number of doses of vaccine (one or two) had no significant impact on waning of immunity. Additionally, although vaccine-induced immunity provided protection from mumps infection for a number of years following receipt of the last dose, immunity waned rapidly after several years and was not associated with receipt of one versus two doses of MMR/MMRV.

Northern Ontario Mumps Outbreak 2017-2018:

A mumps outbreak occurred within two First Nations communities in northern and remote areas of Ontario over the period of December 2017 to June 2018 ⁽⁵²⁾. The outbreak resulted in a total of 70 cases (52 confirmed, 18 probable), with a crude attack rate of 22.3 per 1000. Attack rates were high for many age groups, including infants and adults. The lowest attack rate (8.5 per 1000) was observed among children 1 to < 7 years of age. The median age of cases was 24 years (range 10 months to 62 years). Complications were reported in 7% of cases (5/70) and included orchitis, oophoritis and neurological symptoms. There was one hospitalization and no deaths. At the start of the outbreak, immunization coverage of mumps-containing vaccine among all community members was 46% with two doses and 35% with one dose.

As one component of the public health response, an outbreak dose of mumps-containing vaccine was recommended for individuals aged 8 to 48 years of age (born 1970-2010), not having received MMR vaccine in the last 28 days (based on patient self-report) and no medical contraindications, in addition to opportunistic immunization of under-immunized community members. Among all community members ≥ 1 year of age at the start of the outbreak, 33% received at least one dose of

mumps-containing vaccine during the outbreak period. Thirty-eight percent of those aged 8-48 years at the start of the outbreak received an outbreak dose, and this varied by the number of pre-outbreak vaccine doses (54% uptake among those with no prior doses, 48% among those with one pre-outbreak dose, 31% among those with two pre-outbreak doses, 25% among those with more than two pre-outbreak doses).

An evaluation of the outbreak dose intervention focussed on community members who were age eligible for mumps-containing vaccine (at least one year of age) at the start of the outbreak and defined an outbreak dose as the receipt of any dose of mumps-containing vaccine over the outbreak period. The adjusted hazard ratio for mumps infection among those who did not receive a dose of mumps-containing vaccine during the outbreak was 2.7 (95% confidence interval 1.0-10.1), after adjustment for age group, sex and time since last pre-outbreak dose of vaccine. The data also suggested a dose response relationship between the time since the last pre-outbreak dose and the risk of mumps infection, despite wide and non-significant confidence intervals.

III.5 Molecular Epidemiology of Canadian Outbreaks

According to mumps molecular surveillance from the National Microbiology Lab (NML), all major outbreaks across Canada since 2006 were of genotype G, and nearly all were identical or highly similar to the MuVi/Sheffield.GBR/1.05 WHO reference sequence. This strain is likely endemic, not only in Canada but also elsewhere in North America and Europe. Mumps genotyping involves the sequencing of a small portion of the mumps genome, the small hydrophobic (SH) gene which is only 316 nucleotides in length. Since SH genotyping has been unable to differentiate between outbreaks in Canada in the last decade, sequencing the whole genome (approximately 15,430 nucleotides) may be more informative ^(53, 54).

III.6 Summary of Recent International Outbreaks

Over the last decade, there has been an increase in the reporting of mumps outbreaks in countries with highly vaccinated populations. However, direct comparison between jurisdictions is limited by the differences in case definitions, routine immunization schedules, and epidemiological data collection and reporting. The table below summarizes a sample of reported outbreaks over the last decade.

Country	Size of outbreak	Population affected	Age group	Length of outbreak(s)	Time frame
United States of America ⁽²⁵⁾	Number of cases ranged from 20 to 485 cases per outbreak	Predominately college students and young adults in close contact settings Nearly half the outbreaks (39%) were reported in highly vaccinated populations (coverage for 2 doses $\geq 85\%$).	18-24-year-olds	Total of 23 outbreaks 1.5 to 8.5 months (median = 3 months)	July 2010 to December 2015

Europe (European Centre for Disease Prevention and Control) ⁽⁸⁾	14,795 cases reported by 28 EU/EEA member states	Males more affected than females (57% of all cases)	Highest incidence in 15-19-year-olds (13.2 cases per 100,000 population) Followed by: 10-14-year-olds (12.4 cases per 100,000 population).		2016
Israel ⁽⁵⁵⁾	5239 cases	Majority of cases fully vaccinated (two dose program, 1 and 6 years of age) for their age (78%).	Largest proportion of cases reported in 5-14-year-olds (48% of cases)	12 months	2009-2010

The reported outbreaks affected largely adolescents and young adults in close contact with each other^(56, 57). The higher proportion of adolescents and young adults infected compared to the pre-vaccine era (during which young children were most affected), was explained as a probable consequence of the under-vaccination of children and/or waning immunity in that age group. Close contact settings have also been hypothesized as a factor contributing to the high incidence of mumps among students, particularly in settings in which there is clustering of individuals with relatively low immunization coverage.

IV. VACCINE

IV.1 Preparation(s) Authorized for Use in Canada (e.g., Description, Composition)

There is currently no single-component mumps-containing vaccine available in Canada. All vaccines licensed for the prevention of mumps (MMR and MMRV) in Canada contain the Jeryl Lynn attenuated mumps virus strain that belongs to genotype A:

- **M-M-R[®]II** (live attenuated combined measles, mumps and rubella vaccine), Merck Canada Inc. (MMR)
- **PRIORIX[®]** (live attenuated combined measles, mumps and rubella vaccine), GlaxoSmithKline Inc. (MMR)
- **PRIORIX-TETRA[®]** (live attenuated combined measles, mumps, rubella and varicella vaccine), GlaxoSmithKline Inc. (MMRV)
- **ProQuad[®]** (live attenuated combined measles, mumps, rubella and varicella vaccine), Merck Canada Inc. (MMRV)

For additional information about the mumps vaccines available for use in Canada, refer to the Canadian Immunization Guide, Part 4, Mumps Vaccine at: <https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-14-mumps-vaccine.html>

All of these products have been authorized for a routine two-dose schedule beginning after a child's first birthday. If an early dose of MMR vaccine is provided before 12 months of age (e.g., for travel), then two additional doses are recommended in the product monographs and by NACI ⁽¹⁰⁾. Moreover, the product monograph for Merck's M-M-R[®] II vaccine states that "if concern also exists about immune status regarding mumps or rubella, revaccination with appropriate mumps- or rubella-containing vaccine should be considered" ⁽⁵⁸⁾. The recommendation for a third dose in an outbreak setting is not explicitly mentioned in any product monograph. For outbreak response, MMR vaccine should be used as opposed to MMRV, as in outbreak settings, studies used MMR or monovalent mumps vaccine.

IV.2 Vaccine Effectiveness

Effectiveness of a Jeryl Lynn strain containing MMR vaccine in preventing laboratory-confirmed mumps cases in children and adolescents is estimated to range from 62% to 91% for MMR1 and 76% to 95% for MMR2 ⁽¹⁰⁾. Somewhat lower vaccine effectiveness has been observed in outbreak settings ⁽¹⁹⁾, especially when exposures occurred in close-contact settings ⁽⁵⁹⁾ as protection appears to wane over time ⁽⁶⁰⁾.

NACI reviewed vaccination outcome data following the provision of MMR vaccine, including use of MMR3, reported in 16 publications describing mumps outbreak management interventions in the US, United Kingdom, Israel, Mexico and Norway (see Appendix A). None of the vaccine manufacturers reported any additional non-published information on the effectiveness of MMR vaccine for outbreak management or post-exposure prophylaxis.

Outcomes of interventions in which the MMR vaccine was provided to a defined population in a community were described in two studies. In a community outbreak in a religious community in the US, MMR3 was administered in schools to approximately 65% of 11-17-year-old children ⁽⁶¹⁾. About 98% of the children in the community attended the schools where the vaccine was provided. In the 21 days after the vaccination campaign, a greater than 95% reduction in the mumps attack rate was observed in the vaccinated age group. A statistically significant decline (72.9%) in mumps attack rates was also observed among 5-10-year-old children. Compared to the three weeks before the intervention, the attack rate in the community declined by 76% three weeks post-intervention (from 0.86% to 0.21%). The reported incremental vaccine effectiveness of MMR3 was estimated to be 88% (95%CI: -31.9%-98.9%) at more than three weeks post-immunization. In a similar campaign in the US territory of Guam, an MMR3 dose was administered in schools in which the attack rate was greater than 0.5% (7/64 schools on the island) ⁽⁶²⁾. Over the course of the immunization campaign, over 1,000 children received MMR3 (approximately 5% of children 9-14 years of age living on the island). In this age group, the study authors reported a non-significant difference in attack rates between students that did (0.09%) and did not (0.23%) receive MMR3 (RR=0.4 [95%CI: 0.05-3.5]) at more than three weeks following the intervention.

In the published literature where outcomes were reported, most often MMR vaccine was provided as part of larger institutional outbreak management strategies. In a UK school with 710 students and staff, approximately one fifth of students received an outbreak dose of MMR vaccine (73% received MMR3) ⁽⁶³⁾. The vaccination campaign was initiated one month following the identification of the first case, with the outbreak ending one month following immunization. At more than three weeks after the completion of the vaccination campaign, only two cases of mumps were identified, neither of whom had received an outbreak vaccine dose. In another school outbreak in the UK,

MMR vaccine was provided to children who were found to be susceptible to mumps based on saliva antibody testing⁽⁶⁴⁾. Following the immunization of 28 of 33 susceptible children, no further cases were reported in the school.

One publication from the US CDC also reported an intervention in which 15% (73/541) of individuals with no record of MMR2 vaccination or physician-diagnosed mumps were immunized during an outbreak in a summer camp⁽⁶⁵⁾. At more than two weeks following vaccination, no further cases were reported among campers. In another publication from Mexico, MMR vaccine was provided to resident physicians of 4 hospital departments who did not have a history of mumps. Following an immunization campaign during which 50% to 75%⁽⁶⁶⁾ of residents received the vaccine, no further cases were reported among hospital staff despite an increase in the number of mumps cases in the community. In another publication that described the outcomes of control measures in a hospital setting, MMR vaccine was provided to 14 individuals with no history of mumps or MMR immunization shortly following their contact with an index case⁽⁶⁷⁾. None of these individuals developed mumps after vaccination.

Two publications also reported the outcomes of university-based immunization campaigns that were conducted in the US. During the year-long outbreak that occurred at the University of Illinois⁽⁶⁸⁾, among 50,000 eligible students and staff members (i.e. those born during or after 1957), approximately 11,500 received MMR3. The vaccination campaign was initiated approximately 4.5 months following the initial case report and lasted until the end of the outbreak. Among 317 cases identified during the outbreak, 50 (16%) mumps patients had received MMR3, 232 (73%) received MMR2, 12 (4%) received MMR1, seven (2%) were unvaccinated, and 16 (5%) had unknown vaccination status. Among MMR3 recipients, there were 34 individuals who developed symptoms of mumps two or more weeks after receiving MMR3 and 5 that received MMR3 in years prior the outbreak. During a somewhat shorter (9 months) outbreak at the University of Iowa, MMR3 vaccine was provided to approximately 23% of students^(69, 70) (n≈5,000) within three months of the initial case report. In the 5 months following the intervention, there was an observed three-fold decrease in cases compared to 5 months prior to the intervention. The study authors also reported an incremental MMR3 dose effectiveness (vs. MMR2) of 78% (95%CI: 61-88%). This estimate was somewhat lower (68%; 95%CI: 42.2-82.5%) when only cases that occurred after the campaign initiation were included in the analysis. Among 259 cases identified during the outbreak, 21 developed symptoms of mumps two or more weeks following the receipt of MMR3.

The use of MMR vaccine in confined military settings was also reported in two publications. As a part of the Israeli Defence Forces outbreak management strategy^(55, 71), MMR vaccine was provided to all soldiers in affected units within one week of case identification. During the 2005 outbreak, the vaccine was provided primarily to individuals who had previously received fewer than 2 doses, while during the 2009/10 outbreak all soldiers received the vaccine, independent of their vaccination status. There were no cases identified following immunization during the first outbreak in 2005, and no secondary cases outside of a single incubation period in either of the outbreaks. Similar outcomes were also reported following a report of 10 cases in a Luxembourg military centre⁽⁷²⁾. MMR vaccine was offered to all personnel and trainees in the affected units, after which no further cases were reported.

The outcomes after interventions in which MMR vaccine was provided to contacts of a case were also described in the retrieved publications. In a US study⁽¹⁷⁾, MMR3 was provided to 28 household members of mumps cases within 5 days of the household index-case parotitis onset; no household members became infected with mumps. In another study, among 16 individuals who received MMR1 or MMR2, one adult with no immunization history was diagnosed with mumps during the first incubation period following the index-case onset⁽¹⁷⁾. In comparison, 4 out of 77 individuals with a history of MMR2 who declined a post-exposure dose were diagnosed with mumps. In another outbreak management intervention that was conducted in Norway, a post-exposure MMR3 dose

was provided to approximately 1,300 close contacts of cases ⁽⁷³⁾. In total, only three individuals developed mumps following immunization. One publication describes an intervention in which MMR vaccine was given to contacts of a mumps case on a US naval base ⁽⁷³⁾. Individuals who were considered vaccine and disease naïve based on their infection and laboratory history (mumps IgG antibody titer < 20.0 U/mL) were immunized within 5 days of exposure (8 out of 81). No secondary cases of mumps were observed in any of the exposed individuals after the intervention.

The literature search also identified two older studies that reported on post-immunization outcomes following the administration of a monovalent mumps vaccine containing the Jeryl Lynn strain in settings with significant disease circulation in the US. In one study conducted in 1986, the vaccine was provided to 53/178 previously unimmunized 9- to 12-year-old students during a school outbreak ⁽⁷⁴⁾. In the three weeks following the intervention, cases were reported among both students who received the mumps vaccine (15/53) as well as unimmunized children (51/125). There were no cases reported among immunized students at more than 21 days after receiving the vaccine, compared to 8 cases amongst the unimmunized children. The second study was a randomized controlled study, in which the monovalent vaccine was provided to 502 first and second grade students, while 54 students received placebo ⁽⁷⁵⁾. The vaccination occurred during the field testing of a candidate vaccine in the late 1960's, a time period with significant circulation of the wild-type virus. During the first two weeks post vaccination, there were 28 cases of mumps among immunized students (28/502) and 4 among those who received placebo (4/54). After two weeks, the study authors reported 8 cases of mumps among students who received the vaccine (3 occurring on days 15-30 and 5 at more than 30 days post vaccination) and 16 in the placebo group.

In all of the retrieved publications describing outbreak control measures, MMR vaccination was used as a part of a comprehensive public health response in attempt to control the spread of the disease. In addition to immunization, almost all publications reported the use of case isolation, promotion of appropriate preventive hygiene practices and use of public/media information campaigns as complementary outbreak management measures. The majority of the outbreaks reported the G genotype of mumps virus.

IV.3 Vaccine Safety

While safety outcomes were reported in 7 publications ^(61-63, 68, 76, 77), details of adverse events (AEs) following administration of MMR3 were described in only two studies. None of the studies reported serious AEs following immunization with MMR3. Manufacturers did not report having any additional, non-published, information on the safety of MMR3 vaccine administration.

Abedi et.al and Ogbuanu et al. reported safety outcomes of MMR3 following the vaccination of more than 1,750 students 11-17 years of age ^(61, 77). At least 1 local or systemic AE was reported within 14 days of MMR3 by 7.2% (n=115) of survey respondents. The most commonly reported AEs were injection site pain, redness, or swelling (3.6%); joint or muscle aches (1.8%); dizziness or light-headedness (1.7%); and fever of 38 degrees Celsius or greater (1.3%). In another publication by Nelson et al. the authors reported on the adverse event outcomes following MMR3 immunization of approximately 1,000 children 9-14 years of age. Six percent (32/533) of the survey respondents reported at least 1 local or systemic AEs ⁽⁶²⁾. The most commonly reported AEs were joint aches (2.6%, 14/533), dizziness (2.4%, 13/533) and injection site reactions (2.4%).

Summaries of data from the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) and the US CDC Vaccine Adverse Event Reporting System (VAERS) were also reviewed. In CAEFISS, from more than 15,000 reports for which the dose number of MMR(V) vaccine was available, receipt of MMR3 was identified in only 60 reports (0.4%). Of these, only one AEFI was reported as serious, and concerned a 5-year-old child who was immunized in 2012. The reported AEFI was transverse myelitis lasting 57 days from onset and starting 4 days after

immunization. The infectious disease investigation performed in the hospital yielded a positive test result for parainfluenza 2, which may have been related to the event. The child was reported to have fully recovered. In VAERS, out of approximately 60,000 reports for which the dose number of MMR vaccine was available, about 1,500 reports included MMR3. Of these, 65 (4.4%) AEFIs were reported as serious.

V. DISCUSSION

Since 2016, there has been a substantial increase in the number of reported mumps outbreaks and outbreak-associated mumps cases in Canada. Waning vaccine effectiveness is likely due to decline in cellular immunity, antibody concentrations and avidity. In addition, outbreaks among vaccinated individuals often occur in situations with increased risks for exposure to the virus and transmission may be facilitated through behavioural risk factors.

Epidemiologically, mumps outbreaks can be difficult to characterize especially in community settings. Provincial and Territorial survey data regarding recent mumps outbreaks in Canada, revealed that when vaccination status data were available, roughly half of mumps cases had received at least 2 doses of a mumps containing vaccine. The majority of outbreak-related mumps cases in Canada in recent years have occurred in young adults aged 15-39 years. This contrasts with the pre-vaccine era in Canada when outbreak-related mumps cases occurred most often in children. Geographically, outbreaks in northern Canadian communities have had higher attack rates. While complications of mumps infections are not always well characterized or reported, they are less common in the post-vaccine era and among those vaccinated.

The NACI literature review identified 16 publications where an additional dose of MMR vaccine was used as a control measure in an outbreak setting. Three main immunization approaches were described in these studies: 1) vaccination of a specific population group (typically an age group with a high disease attack rate); 2) vaccination of a specific community within a defined geographical setting (i.e., university students and staff), and 3) vaccination of close contacts (post exposure immunization in closed settings). These studies described varied immunization strategies (e.g., time to vaccine program implementation, population, setting, additional outbreak control measure) with varied coverage. The quality of the studies ranged from fair to low. Overall, the evidence suggested that an additional MMR dose seemed likely to reduce disease burden, however, pooled estimates of vaccine effectiveness could not be determined due to heterogeneity in study designs.

At the population level, there was some evidence that administration of additional MMR doses is likely to affect transmission and consequently the duration and size of an outbreak, particularly if given early in the course of the outbreak and when a high vaccine uptake is achieved in the target group.

At an individual level, following the receipt of MMR vaccine in an outbreak setting, onset of symptomatic mumps disease was rarely observed more than two weeks post-immunization and rarely outside of a single incubation period. The results of a small number of studies that provided MMR3 vaccine to close contacts of a case suggested that a dose provided within a week post-exposure may be effective in preventing symptomatic disease and transmission. However, ideal timing of a post-exposure dose was not specified. Several studies also suggested that acceptability to receive additional doses of MMR vaccine is likely to be increased during outbreaks and among individuals who are perceived to be at higher risk of mumps and its complications.

Safety outcomes were reported in 7 publications identified in the literature review. These studies did not identify any associated serious AEs following a third dose of MMR vaccine in an outbreak setting. This was based on data following the administration of >14,000 MMR3 doses in the

reviewed studies. These findings are consistent with previous observations of lower frequency and intensity of AEs with subsequent doses. No unexpected safety signals were identified. Most systemic and local adverse events, particularly among previously vaccinated individuals, were mild in intensity and short in duration (lasting 1–3 days).

More robust, comprehensive and consistent evidence is needed on the effectiveness of use of outbreak doses of mumps-containing vaccine in situations similar to those observed in Canada. Therefore, NACI will continue to monitor the body of evidence related to the effectiveness and safety of MMR vaccine when provided in mumps outbreak settings, including off-label administration of MMR3 for outbreak control, and will update this statement as needed.

VI. RECOMMENDATIONS

Following the review of available evidence on the burden of illness from mumps disease and outbreaks in Canada, as well as the effectiveness and the safety of additional MMR vaccine doses in outbreak settings, NACI makes the following recommendations for public health level decision-making. The recommendations are consistent with national goals for mumps disease reduction and vaccination targets for mumps in order to maintain less than 100 annual cases⁽²⁾, based on a 5-year rolling average.

A *strong recommendation* applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present. A *discretionary recommendation* may be considered for some populations/individuals in some circumstances. Alternative approaches may be reasonable. Please see Table 3 for a more detailed explanation of strength of NACI recommendations and grade of the body of evidence.

VI.1 Recommendations for Public Health Program Level Decision-Making (i.e., Provinces/Territories Making Decisions for Publicly Funded Immunization Programs)

In considering these recommendations and for the purposes of publicly funded immunization program implementation, provinces and territories may take into account multiple factors, such as cost-benefit evaluation, the local epidemiology of mumps, and other local programmatic and operational factors (e.g., current immunization programs, resources, outbreak control measures).

Recommendation 1: NACI recommends that an outbreak dose of MMR vaccine may be considered in an outbreak setting. (Discretionary Recommendation)

- **NACI concludes there is fair evidence to recommend MMR vaccine use (including catch-up vaccination with or without MMR3) during outbreaks (Grade B Evidence)**

Summary of Evidence and Rationale

- An outbreak dose of MMR vaccine is likely to be effective in reducing the size and duration of the outbreak.
- A third dose is recommended for those who have previously received 2 doses of mumps-containing vaccine after their first birthday, particularly if the last dose of MMR vaccine was received 10 years ago or more.
- For those with unknown immunization status, an outbreak dose can be provided. There is no evidence to support providing an additional dose if three doses have been previously received after the first birthday.

- Other factors beyond number of doses, such as the time since last dose may also be important factors when considering outbreak vaccination control measures.
- Decisions on when and in what context to implement an outbreak/third dose recommendation are complex and require additional input on mumps outbreak response. Refer to the management options table.
- A broad, non-discriminatory recommendation for an outbreak dose simplifies program implementation (e.g., vaccination status may not be easily determined) and increases coverage.
- Increasing immunizations during mumps outbreaks is consistent with the public health management approach taken for other vaccine preventable disease outbreaks.
- The vaccine effectiveness of an outbreak dose could not be determined based on the currently available evidence, in part due to differences in study designs.
- In the setting of a mumps outbreak, MMR vaccine should be provided (not MMRV since it has not been studied in an outbreak setting). Although product monographs for MMR vaccines do not explicitly indicate the use of a third dose in an outbreak setting, MMR3 has been used as a strategy for outbreak control in many jurisdictions outside of Canada and with formal recommendations from some immunization advisory committees. Furthermore, no vaccine safety concerns for MMR3 were identified in this review. Therefore, based on the balance of beneficence and non-maleficence, NACI considers this an appropriate intervention to prevent disease in an outbreak setting, despite the current wording of product monographs.

Recommendation 2: NACI recommends that providing MMR vaccine up to a third dose to close contacts following exposure to a case of mumps may be considered in an outbreak setting (Discretionary Recommendation)

- **NACI concludes there is insufficient evidence for or against recommending a dose of mumps-containing vaccine to close contacts following exposure to a case of mumps (Grade I Evidence).**

Summary of Evidence and Rationale

- Evidence for recommending MMR vaccine to close contacts following exposure to a case of mumps is of poor quality.
- MMR vaccine may prevent symptomatic disease if administered shortly following exposure. The time period by which a post-exposure dose needs to be provided to prevent infection when already exposed is not known.
- Providing MMR vaccine to close contacts may be considered as an intervention for disease control in the setting of sporadic (non-outbreak) cases, and/or as an opportunity to provide an outbreak dose to at-risk groups in outbreak settings.
- This use of MMR vaccine for close contacts is consistent with the use of vaccines for contacts of other vaccine preventable diseases, either as post-exposure prophylaxis or using contact follow-up as an opportunity to update immunizations.

VII. MANAGEMENT OPTIONS

Mumps is spread through direct contact with saliva by sharing drinks or kissing, or by large droplet transmission via coughing or sneezing. The incubation period for mumps ranges from 14 to 25 days. Once an individual is infected, mumps can be communicable from 2 days before to 5 days after the onset of parotitis ⁽⁷⁸⁾. Mumps cases can also be asymptomatic but remain infectious to others.

The size, scope and duration of mumps outbreaks can be variable and their progression and peak is difficult to predict given delays in reporting, health seeking behaviours, and the relatively long incubation period for the mumps virus. Furthermore, circulation of mumps virus in highly immunized populations may be undetected and determining immunization status of cases and contacts may be challenging in many jurisdictions in Canada due to variability in the availability of comprehensive immunization registries. The public health response to mumps includes management of cases and contacts and identifying social networks to define the at-risk population when contact follow-up is not feasible; and maintaining/enhancing surveillance for further cases and disease outcomes (e.g., hospitalizations, complications). Generally, a mumps outbreak is controlled by:

- Defining the at-risk population(s) and transmission setting(s);
- Preventing further transmission through isolation of cases and contact education/awareness;
- Vaccination of under-immunized groups; and
- Good risk communication ⁽¹¹⁾.

In an outbreak setting, implementation of MMR immunization strategies may be considered as a part of outbreak management. The MMR vaccine is considered to be safe with the majority of systemic or local adverse events being mild in intensity and limited in duration (lasting 1–3 days), particularly in previously vaccinated individuals. Immunization in an outbreak setting leads to the boosting of humoral and cellular immunity which can assist with outbreak control.

Various options for the implementation of the NACI recommendation for an outbreak dose of MMR vaccine are available, including immunization according to time since last dose, setting and intensity of exposure, and age and risk of complications. Understanding the nature of the outbreak (person-place-time) as well as ease of access to the immunization history of individuals within the target group are important for informing the choice and delivery of the outbreak dose strategy, including whether the immunization strategy is operationalized as a focus on under-immunized groups (i.e. delivery of a first or second dose), immunizing with a third dose of mumps-containing vaccine (i.e. in outbreak settings with high two dose coverage), or whether it is operationalized as delivery of an outbreak dose in settings where access to individual vaccination status to determine eligibility for a specific dose number of MMR is challenging and/or when the population at risk includes both one and two dose vaccinated individuals.

Implementation of outbreak-related immunization strategies early during a mumps outbreak (during the time of rapidly increasing case counts) is important, as early vaccination is likely to be the most effective intervention to control the outbreak. While immunization in later stages of the outbreak (e.g., following the peak of the outbreak) may benefit individuals, its effect at the population-level is uncertain. In order to minimize logistical challenges at the local level, particularly in outbreaks occurring in isolated and hard to reach communities, early coordination with provincial/territorial immunization program contacts is recommended.

In individuals for whom immunization history can be verified, immunization according to time since last dose should be considered. Vaccine effectiveness has been observed to wane over time, likely

due to the declines in cellular immunity, antibody concentrations and avidity. The risk of mumps in outbreak settings has been observed to increase starting at 2 years following the last MMR dose with significant increases at more than 10 years after last MMR vaccination. Therefore, individuals who received their last dose of MMR vaccine > 10 years ago are at greatest risk of mumps infection and should be prioritized for vaccination in outbreak settings, where this is feasible to operationalize.

In groups for whom the risk of exposure or exposure history can be determined, targeted immunization may simplify program delivery. The majority of outbreaks in Canada and internationally have been observed in close contact settings in which the level of exposure (duration and intensity) to the mumps virus is increased. These have typically included households, educational institutions, sports facilities, and smaller communities. An outbreak dose of MMR vaccine provided to individuals in a defined setting may be effective in reducing mumps incidence in the setting.

When determining vaccination status or exposure risk is challenging, immunization of age groups who are known to historically have the highest attack rates and risks of complications may be another option for rapid program implementation. Immunization of age specific groups has been effective in reducing both mumps incidence in specific age groups as well as the overall disease burden in the community. Based on surveillance data obtained from the Canadian Notifiable Disease Surveillance System (CNDSS), over the period of 2014-2018, the majority of cases were observed in the 20- to <40-year-old age group, with the highest incidence observed among adults 20-24 years (3.8 cases per 100,000 population).

The decision on which immunization strategy is most appropriate for a specific outbreak will depend on the considerations summarized above, which are further outlined in the table below and through future updates to PHAC's Mumps Outbreak Control guidance ⁽¹¹⁾.

Management Options Table

	Considerations	Decision Points
1. Immunization according to time since last dose	<ul style="list-style-type: none"> Vaccine effectiveness has been observed to wane over time, likely due to the declines in cellular immunity and antibody concentrations and avidity^(14, 16, 17, 20). The risk of mumps outbreaks has been observed to increase starting at 2 years following the last MMR dose, and significantly increasing at more than 10 years after the last MMR vaccination^(70, 79). Mathematical models suggest that up to 25% of vaccinated individuals may be susceptible to mumps within 7.9 years (95% CI, 4.7 to 14.7 years), and 50% within 19 years (95% CI, 11.2 to 35.4 years) following the last mumps-containing vaccine dose⁽²⁰⁾. Determining vaccination status may be challenging, as records might be missing or incomplete or not available. This can complicate the implementation of an outbreak dose strategy that requires knowledge of time since last dose, resulting in barriers in the delivery of an outbreak dose. 	<ul style="list-style-type: none"> Individuals who have received the last dose of MMR vaccine > 10 years are at greatest risk of mumps and should be prioritized for vaccination. Implementation of an outbreak dose strategy that requires knowledge of time since last dose can be complicated and result in barriers in the timely delivery of immunization. In some settings this information may be difficult to obtain. The vaccine is immunogenic and safe with no associated serious adverse events reported in immunocompetent individuals.
2. Immunization according to setting and level of exposure	<ul style="list-style-type: none"> The majority of outbreaks in Canada and internationally have been observed in closed contact settings in which the level of exposure (duration and intensity) to the mumps virus is increased. These have typically included households, educational institutions, sports facilities, and smaller communities. There is evidence that an outbreak dose of MMR vaccine provided to individuals in a defined setting may be effective in reducing the incidence of infection following the outbreak dose campaign⁽⁸⁰⁾. Immunization of individuals within a defined setting may simplify vaccine delivery. 	<ul style="list-style-type: none"> Outbreak immunization strategies focused on a particular setting or level of exposure is likely to contribute to the reduction of the disease burden in the wider community. If a mumps outbreak is occurring in a defined setting; immunization of all individuals within the setting may simplify delivery.
3. Immunization according to age and risk of complications	<ul style="list-style-type: none"> In Canada, based on surveillance data obtained from the Canadian Notifiable Disease Surveillance System (CNDSS), the majority of cases have been 	<ul style="list-style-type: none"> In situations where vaccination or exposure status of affected individuals may not be readily known, provision of additional

	<p>observed in the 20- to <40-year-old age group in recent years (2014-2018). During this time period, the highest incidence rates were reported in adults 20-24 years (3.8 cases per 100,000 population).</p> <ul style="list-style-type: none"> • Severity of disease and the risk of complications ⁽⁸⁰⁾ is typically higher among post-pubertal youth and adults, though reduced compared to pre-vaccine era. • In outbreaks where there is no defined setting or exposure group (e.g., a community outbreak), vaccinating age cohorts that are at highest risk may be considered. • Targeted immunization of age groups with the highest attack rates has shown to be effective in reducing the age group-specific and overall disease burden in the community. 	<p>doses is safe and is likely to increase individual protection.</p> <ul style="list-style-type: none"> • In large community outbreaks, determination of exposure (contact tracing) and vaccination status may not be practical and may quickly overwhelm available public health resources ⁽⁸¹⁾. • Outbreak immunization programs focusing on a particular population group, particularly those with highest observed attack rates, is likely to contribute to the reduction of the disease burden in the wider community. • The acceptability of additional doses of MMR vaccine is likely to be increased during outbreaks and among individuals who perceive themselves to be at higher risk of mumps and its complications.
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VIII. KNOWLEDGE GAPS AND RESEARCH PRIORITIES

After careful review of available evidence, NACI has identified the need for further research to address current knowledge gaps where data are absent or limited. NACI recognizes that there are studies already in progress that may address many of these gaps, but the findings of these studies were not yet available at the time of review. Identified knowledge gaps include:

- Examining the cost of different public health measures to contain a mumps outbreak in different settings and evaluating the cost-effectiveness of various options for the implementation of an additional mumps outbreak dose strategy
- Modeling the effect of an additional dose of MMR vaccine on the burden of mumps during a mumps outbreak
- Obtaining more comprehensive/complete national data on the epidemiology of and response to mumps outbreaks
- The absolute effectiveness of immunization with an outbreak dose of mumps-containing vaccine in reducing disease burden
- A more thorough understanding of the duration of immunity and waning of immunity and how this is impacted by the administration of additional outbreak doses of mumps-containing vaccine
- The immunologic correlates of protection from disease and the impact of an additional outbreak dose of mumps-containing vaccine on the immunologic response
- The optimal timing of the outbreak dose
- The protection offered by the vaccine strain as compared to the circulating strain of mumps in Canada

IX. SURVEILLANCE ISSUES

The following issues relating to mumps outbreak surveillance in Canada have been identified:

- The national surveillance data for mumps has numerous limitations, including incomplete variables (age, gender, onset date), timeliness and limited availability of information on vaccination status, disease severity, including complications and long-term sequelae.
- Data on outbreaks in Canada is not routinely collected through national surveillance.
- Given that there is no standard national outbreak case definition, categorization of cases as outbreak-related is left to the discretion of each jurisdiction.
- Due to asymptomatic infection and non-specific symptoms, it is often challenging to identify the source of infection for cases, with limited detail on setting-specific acquisition information in surveillance data as a result.
- Ascertaining mumps genome sequencing to assist in outbreak characterization and transmission patterns.

TABLES

Table 1: Ranking Individual Studies: Levels of Evidence Based on Research Design

Level	Description
I	Evidence from randomized controlled trial(s).
II-1	Evidence from controlled trial(s) without randomization.
II-2	Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group using clinical outcome measures of vaccine efficacy.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.

Table 2: Ranking Individual Studies: Quality (internal validity) Rating of Evidence

Quality Rating	Description
Good	A study (including meta-analyses or systematic reviews) that meets all design- specific criteria* well.
Fair	A study (including meta-analyses or systematic reviews) that does not meet (or it is not clear that it meets) at least one design-specific criterion* but has no known "fatal flaw".
Poor	A study (including meta-analyses or systematic reviews) that has at least one design-specific* "fatal flaw", or an accumulation of lesser flaws to the extent that the results of the study are not deemed able to inform recommendations.

* General design specific criteria are outlined in Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med 2001; 20: 21–35.

Table 3: NACI Recommendations: Strength of Recommendation and Grade of Evidence

STRENGTH OF NACI RECOMMENDATION	GRADE OF EVIDENCE
Based on factors not isolated to strength of evidence (e.g., public health need)	Based on assessment of the body of evidence
<p>Strong “should/should not be offered”</p> <ul style="list-style-type: none"> ➤ Known/Anticipated advantages outweigh known/anticipated disadvantages (“should”), OR Known/Anticipated disadvantages outweigh known/anticipated advantages (“should not”) ➤ Implication: A strong recommendation applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present 	A - <i>good evidence</i> to recommend
	B – <i>fair evidence</i> to recommend
	C – <i>conflicting evidence</i> , however other factors may influence decision-making
	D – <i>fair evidence</i> to recommend against
	E – <i>good evidence</i> to recommend against
	I – <i>insufficient evidence</i> (in quality or quantity), however other factors may influence decision-making
<p>Discretionary “may be considered”</p> <ul style="list-style-type: none"> ➤ Known/Anticipated advantages closely balanced with known/anticipated disadvantages, OR uncertainty in the evidence of advantages and disadvantages exists ➤ Implication: A discretionary recommendation may be considered for some populations/individuals in some circumstances. Alternative approaches may be reasonable. 	A - <i>good evidence</i> to recommend
	B – <i>fair evidence</i> to recommend
	C – <i>conflicting evidence</i> , however other factors may influence decision-making
	D – <i>fair evidence</i> to recommend against
	E – <i>good evidence</i> to recommend against
	I – <i>insufficient evidence</i> (in quality or quantity), however other factors may influence decision-making

LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
CI	Confidence of Interval
CDC	Centres for Disease Control and Prevention (United States)
CNDSS	Canadian Notifiable Disease Surveillance System
MMR	Measles-mumps-rubella vaccine
MMRV	Measles-mumps-rubella-varicella vaccine
MMR1	First dose of MMR vaccine
MMR2	Two-dose MMR vaccination
MMR3	Third dose of MMR vaccine
NACI	National Advisory Committee on Immunizations
PHAC	Public Health Agency of Canada
PT	Provinces and Territories
RCT	Randomized controlled trial
SAE	Serious adverse event
US	United States
VAERS	Vaccine Adverse Events Reporting System
WG	Working Group (NACI MMR)

ACKNOWLEDGMENTS

This statement was prepared by: Dr. O Baclic, Dr. M Salvadori, Ms. A Sinilaite, Dr. L Zhao, Dr. V Dubey, and approved by NACI.

NACI gratefully acknowledges the contribution of: Ms. B Ho Mi Fane, Ms. S Kelly, Ms. D MacDonald, Mr. M Roy, Ms. M Saboui, Ms. S Squires, Dr. M Tunis, Lynda Gamble (Health Library, HC), Ms. C Tremblay.

NACI Members: Dr. C Quach (Chair), Dr. S Deeks (Vice-Chair), Dr. N Dayneka, Dr. P De Wals, Dr. V Dubey, Dr. R Harrison, Dr. K Hildebrand, Dr. J Papenburg, Dr. C Rotstein, Dr. B Sander, Ms. S Smith, Dr. S Wilson

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APPENDIX A: SUMMARY OF EFFECTIVENESS FINDINGS

Study Details					Summary	
Publication	Vaccine (dose provided), Strain	Study Design	Outbreak and study description	Summary of Key Findings	Level of Evidence	Quality
Aasheim E, Inns T, Trindall A, Emmett L, Brown K, Williams C, et al. Outbreaks of mumps in a school setting, United Kingdom, 2013. Hum Vaccin Immunother. 2014;10(8):2446-9.	MMR1, MMR2, MMR3; Jeryl Lynn strain	Case series	<ul style="list-style-type: none"> • <u>Outbreak location</u>: UK (East of England; exact school location not provided) • <u>Duration of outbreak</u>: January 1 - April 13, 2013 • <u>Size of outbreak</u>: 28 cases; median age 14 years • <u>Population at risk</u>: students 10-19 years of age (n=540) and staff (n=170) of an unnamed school • <u>Time of intervention</u>: February 12-14, 2013 • <u>Intervention group</u>: 110 students 10-19 years of age whose parents approved the administration of an additional MMR dose • <u>Other</u>: 84% of cases with history of MMR2; MMR schedule in UK: 12 months and 3-5 years of age 	<p>Attack rates by age group:</p> <ul style="list-style-type: none"> - students 15-16 years of age: 13.7% - students 13-14 years of age: 8.5% - students 14-15 years of age: 5% <p>Out of 103 students vaccinated in school, 76 received MMR3.</p> <p>Out of 13 cases that were reported after the completion of the immunization campaign, only one occurred in a student that received an outbreak dose; symptom onset was less than 2 weeks after vaccination.</p> <p>Because the majority of new cases (n=11/13) occurred within 3 weeks after the immunization campaign (during the typical disease incubation period), study authors were not able to make conclusions regarding the effectiveness of the intervention.</p>	II-3	Fair
	MMR3; Jeryl Lynn strain	Case series	<ul style="list-style-type: none"> • <u>Outbreak location</u>: US (University of Illinois at Urbana-Champaign, IL) • <u>Duration of outbreak</u>: April 9, 2015 - May 27 2016 • <u>Size of outbreak</u>: 317 cases; median age, 20 years • <u>Population at risk</u>: approximately 50,000 students and staff • <u>Time of intervention</u>: vaccination provided in the summer (August 6 to 27, 2015), as well as during fall and spring (2016) semesters 	<p>A total of 8,200 doses were administered at vaccination clinics on the university campus during the summer months, and 3,300 doses through the fall (2015) and spring (2016) semesters. Additional doses (number unknown) were provided to students and staff members living off campus during the summer.</p> <p>Out of 45 cases who received MMR3 during the outbreak, 60% (n=27) received it >4 weeks prior to symptom onset. 5 cases received MMR3 in years prior the outbreak.</p>	II-3	Fair

Study Details					Summary	
Publication	Vaccine (dose provided), Strain	Study Design	Outbreak and study description	Summary of Key Findings	Level of Evidence	Quality
Aasheim E, Inns T, Trindall A, Emmett L, Brown K, Williams C, et al. Outbreaks of mumps in a school setting, United Kingdom, 2013. Hum Vaccin Immunother. 2014;10(8):2446-9.	MMR1, MMR2, MMR3; Jeryl Lynn strain	Case series	<ul style="list-style-type: none"> • <u>Outbreak location</u>: UK (East of England; exact school location not provided) • <u>Duration of outbreak</u>: January 1 - April 13, 2013 • <u>Size of outbreak</u>: 28 cases; median age 14 years • <u>Population at risk</u>: students 10-19 years of age (n=540) and staff (n=170) of an unnamed school • <u>Time of intervention</u>: February 12-14, 2013 • <u>Intervention group</u>: 110 students 10-19 years of age whose parents approved the administration of an additional MMR dose • <u>Other</u>: 84% of cases with history of MMR2; MMR schedule in UK: 12 months and 3-5 years of age 	<p>Attack rates by age group:</p> <ul style="list-style-type: none"> - students 15-16 years of age: 13.7% - students 13-14 years of age: 8.5% - students 14-15 years of age: 5% <p>Out of 103 students vaccinated in school, 76 received MMR3.</p> <p>Out of 13 cases that were reported after the completion of the immunization campaign, only one occurred in a student that received an outbreak dose; symptom onset was less than 2 weeks after vaccination.</p> <p>Because the majority of new cases (n=11/13) occurred within 3 weeks after the immunization campaign (during the typical disease incubation period), study authors were not able to make conclusions regarding the effectiveness of the intervention.</p>	II-3	Fair
	MMR3; Jeryl Lynn strain	Case series	<ul style="list-style-type: none"> • <u>Outbreak location</u>: US (University of Illinois at Urbana-Champaign, IL) • <u>Duration of outbreak</u>: April 9, 2015 - May 27 2016 • <u>Size of outbreak</u>: 317 cases; median age, 20 years • <u>Population at risk</u>: approximately 50,000 students and staff • <u>Time of intervention</u>: vaccination provided in the summer (August 6 to 27, 2015), as well as during fall and spring (2016) semesters 	<p>A total of 8,200 doses were administered at vaccination clinics on the university campus during the summer months, and 3,300 doses through the fall (2015) and spring (2016) semesters. Additional doses (number unknown) were provided to students and staff members living off campus during the summer.</p> <p>Out of 45 cases who received MMR3 during the outbreak, 60% (n=27) received it >4 weeks prior to symptom onset. 5 cases received MMR3 in years prior the outbreak.</p>	II-3	Fair

<p>Albertson JP, Clegg WJ, Reid HD, Arbise BS, Pryde J, Vaid A, Thompson-Brown R, Echols F. Mumps outbreak at a university and recommendation for a third dose of measles-mumps-rubella vaccine- Illinois, 2015-2016. MMWR Morb Mortal Wkly Rep.. 2016;65(29):731-4.</p>			<ul style="list-style-type: none"> • <u>Intervention group</u>: university students and staff born during or after 1957 • <u>Other</u>: 73% (n=232) of cases with history of MMR2; genotype G isolated from the tested samples (n=4) 			
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<p>Wharton M, Cochi SL, Hutcheson RH, Bistowish JM, Schaffner W. A large outbreak of mumps in the postvaccine era. J Infect Dis. 1988 Dec;158(6):1253-60.</p>	<p>Monovalent mumps vaccine</p>	<p>Cohort</p>	<ul style="list-style-type: none"> • <u>Outbreak location</u>: US (Unnamed high school A) • <u>Duration of outbreak</u>: 25 August to 14 November, 1986 • <u>Size of outbreak</u>: 332 cases • <u>Population at risk</u>: 1,764 9-12 grade students • <u>Time of intervention</u>: vaccine provided on October 6, 1986 • <u>Intervention group</u>: 414 students and staff not previously immunized with one dose of mumps vaccine • <u>Other</u>: Peak of outbreak registered on September 30th 	<p>178 susceptible students (negative history of either mumps disease or mumps vaccination) were followed until the end of the outbreak. 53/178 students received mumps vaccine during the outbreak. 15/53 immunized and 51/125 unimmunized students developed mumps between one and 21 days after the immunization clinic. The majority (13/15) of mumps cases in immunized students occurred within 14 days of the immunization clinic. Among the remaining 112 students, no subsequent cases of mumps occurred >22 days following vaccine administration among the 38 immunized students, whereas 8/74 unimmunized students acquired mumps. Based on these findings, authors concluded that a dose of monovalent mumps vaccine has an impact on controlling the outbreak.</p>	<p>II-2</p>	<p>Fair</p>
<p>Ramsay ME, Brown DW, Eastcott HR, Begg NT. Saliva antibody testing and vaccination in a mumps outbreak. CDR (Lond Engl Rev). 1991 Aug 16;1(9):R96-8</p>	<p>MMR vaccine, not specified</p>	<p>Cohort</p>	<ul style="list-style-type: none"> • <u>Outbreak location</u>: UK (Unnamed 2 elementary) • <u>Duration of outbreak</u>: October 1988 to March 1989 • <u>Size of outbreak</u>: 29 cases • <u>Population at risk</u>: 33 students who were deemed susceptible based on saliva antibody testing; overall student population in both schools - 368 children 5 – 9 years of age • <u>Time of intervention</u>: vaccine provided to 28/33 children at 22-25 weeks post index case diagnosis • <u>Intervention group</u>: students • <u>Other</u>: Peak of outbreak occurred at 15 weeks post index case diagnosis 	<p>No new cases of mumps were reported following the immunization of susceptible children</p>	<p>II-3</p>	<p>Fair</p>

Sugg WC, Finger JA, Levine RH, Pagano JS. Field evaluation of live virus mumps vaccine. J Pediatr. 1968 Apr;72(4):461-6	Monovalent mumps vaccine; Jeryl Lynn strain	RCT	<ul style="list-style-type: none"> • <u>Outbreak location</u>: Forsyth County, North Carolina (US) <p>The study field tested the formulation of the Jeryl Lynn strain that is currently contained in the MMR vaccine.</p> <p>The monovalent vaccine was administered to 2,965 children attending 1st and 2nd grade of elementary school; 329 children received placebo.</p>	<p>Cases 1-14 days post vaccination:</p> <ul style="list-style-type: none"> • 28 immunized • 4 placebo • 14 unimmunized <p>Cases 15-30 days post vaccination:</p> <ul style="list-style-type: none"> • 3 immunized • 3 placebo • 10 unimmunized <p>Cases >30 days post vaccination:</p> <ul style="list-style-type: none"> • 5 immunized • 13 placebo • 45 unimmunized 	I	Fair
Fischer PR, Brunetti C, Welch V, Christenson JC. Nosocomial mumps: report of an outbreak and its control. Am J Infect Control. 1996 Feb;24(1):13-8.	MMR vaccine, not specified	Cohort	<ul style="list-style-type: none"> • <u>Outbreak location</u>: US (Shriners Hospital) • <u>Duration of outbreak</u>: April 26, 1994 to May 22, 1994 • <u>Size of outbreak</u>: 4 cases • <u>Population at risk</u>: Hospital patients and staff • <u>Time of intervention</u>: MMR vaccine provided following exposure to index case • <u>Intervention group</u>: vaccine provided to 14 individuals with no history of clinical mumps 	None of the immunized individuals developed mumps	II-3	Fair
Pérez-Alba E, García-Ortiz A, Salazar-Montalvo RG, Hernández-Guedea MA, Camacho-Ortiz A. Mumps outbreak with high	MMR vaccine, not specified	Cohort	<ul style="list-style-type: none"> • <u>Outbreak location</u>: Mexico (University Hospital) • <u>Duration of outbreak</u>: October 2017 to April 2017 • <u>Size of outbreak</u>: 9 cases • <u>Population at risk</u>: HCW >21 years of age without history of mumps 	No further cases occurred among hospital residents despite an increase in the number of community cases.	II-3	Fair

complication rates among residents in a university teaching hospital. Am J Infect Control. 2019 Mar;47(3):337-339.			<ul style="list-style-type: none"> • <u>Time of intervention</u>: March 2017 • <u>Intervention group</u>: MMR vaccine offered to all medical residents • <u>Other</u>: Coverage of at least 1 new dose was achieved in 75% of internal medicine residents, 51% of surgery residents, 67% of radiology residents and 66% of in pediatrics residents. 			
<p>Mossong J, Bonert C, Weicherding P, Opp M, Reichert P, Even J, Schneider F.</p> <p>Mumps outbreak among the military in Luxembourg in 2008: epidemiology and evaluation of control measures. Euro Surveill. 2009 Feb 19;14(7):19121.</p>	Outbreak dose of MMR (Priorix)	Cohort	<ul style="list-style-type: none"> • <u>Outbreak location</u>: Luxembourg military centre • <u>Duration of outbreak</u>: September 8 to November 02, 2008 • <u>Size of outbreak</u>: 10 cases • <u>Population at risk</u>: not specified • <u>Time of intervention</u>: 28 October, 2008 • <u>Intervention group</u>: personnel and trainees in units on the affected military site • <u>Other</u>: Approximately half of vaccine recipients were IgG positive prior to the immunization campaign. 	While no clinical cases were observed at the military centre following immunization, clinical cases continued to be reported in the Luxembourg "civilian" population.	II-3	Fair
Centers for Disease Control and Prevention (CDC). Mumps outbreak at a summer camp - New York, 2005. MMWR Morb Mortal Wkly Rep. 2006 Feb 24;55(7):175-7	MMR1/2	Cohort	<ul style="list-style-type: none"> • <u>Outbreak location</u>: US • <u>Duration of outbreak</u>: June 30 to August 18, 2005 • <u>Size of outbreak</u>: 31 cases • <u>Population at risk</u>: 541 campers and staff members • <u>Time of intervention</u>: August 2005 • <u>Intervention group</u>: 73 individuals with no record of immunization or with documented record of only one dose of MMR vaccine • <u>Other</u>: Peak of outbreak occurred on July 20. 	No further clinical cases were reported following the intervention.	II-3	Fair

<p>Cardemil CV, Dahl RM, James L, Wannemuehler K, Gary HE, Shah M, Marin M, Riley J, Feikin DR, Patel M, Quinlisk P. 2017. Effectiveness of a third dose of MMR vaccine for mumps outbreak control. N Engl J Med. 2017;377(10):947-56.</p> <p>Shah M, Quinlisk P, Weigel A, Riley J, James L, Patterson J, Hickman C, Rota PA, Stewart R, Clemmons N, Kalas N, Cardemil C, et al. 2018. Mumps Outbreak in a Highly Vaccinated University-Affiliated Setting before and after a Measles-Mumps-Rubella Vaccination Campaign-Iowa, July 2015-May 2016. Clin Infect Dis. 2018;66(1):81-8..</p>	<p>MMR1, MMR2, MMR3; Jeryl Lynn strain</p>	<p>Cohort</p>	<ul style="list-style-type: none"> • <u>Outbreak location</u>: US (University of Iowa) • <u>Outbreak observation period</u>: 24 August, 2015 - 13 May, 2016 • <u>Affected population group</u>: 20,496 university students and staff • <u>Size of outbreak</u>: 259 cases; median age, 21 years • <u>Time of intervention</u>: November 10 - 19, 2015 • <u>Intervention group</u>: students < 25 years of age • <u>Intervention setting</u>: University of Iowa • <u>Other</u>: 85% (n=221) of cases with history of MMR2 	<p>A total of 4,783 received MMR3 (94% provided during the vaccination campaign)</p> <p>Attack rates according to number of MMR doses:</p> <ul style="list-style-type: none"> • students receiving MMR3: 0.67% • students with MMR2: 1.45% • students with MMR1: 3.28% <p>Attack rates according to the timing of MMR2 dose:</p> <ul style="list-style-type: none"> • if <2 years: 0.16% • if 3-12 years: 0.39% • if 13-15 years: 1.13% • if 16-23 years: 1.76% <p>Risk of mumps (HR) according to the time since MMR2 (reference: 0-2 years):</p> <p>if 3-12 years: 3.1 (95% CI: 0.6-16.2)</p> <p>if 13-15 years: 9.1 (95%CI: 2.2-36.9)</p> <p>if 16-24 years: 14.3 (95%CI: 3.5-57.6)</p> <p>Incremental VE (MMR3 vs. MMR2): ranged from 60.0% (95% CI, 38.4 -74.0%) at 7 days after vaccination to 78.1% (95% CI: 60.9- 87.8%) at 28 days after vaccination</p> <p>Out of 34 cases who received MMR3 during the outbreak, 35% (n=12) received it >4 weeks prior to symptom onset.</p>	<p>II-2</p>	<p>Fair</p>
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Fiebelkorn AP, Lawler J, Curns AT, Brandenburg C, Wallace GS. Wallace 2013. Mumps postexposure prophylaxis with a	MMR1, MMR2, MMR3; Jeryl Lynn strain	Cohort	<ul style="list-style-type: none"> • <u>Outbreak location</u>: US (NY state, Orange County) • <u>Duration of outbreak</u>: September 2009-June 2010 • <u>Size of outbreak</u>: 49 index case-patients; median age, 9 years 	<p>28 household members received MMR3 and 16 received MMR1 or MMR2. 77 household members with MMR2 who declined MMR3 immunization were used as controls.</p> <p>Attack rates (12-25 days after parotitis onset in the index-case) according to MMR3 status*:</p> <p>- intervention group: 0% (0/28)</p>	II-2	Fair
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third dose of measles-mumps-rubella vaccine, Orange County, New York, USA. Emerg Infect Dis, 19(9): 1411-7.			<ul style="list-style-type: none"> • <u>Population at risk</u>: 239 household members of index- case-patients • <u>Time of intervention</u>: February 24 - April 24, 2010 • <u>Intervention group</u>: household members of index case-patients if onset of disease was <5 days • <u>Comparison group</u>: household members of cases who declined vaccination 	<p>- control group: 5.2% (4/77)</p> <p>*difference between groups was not statistically significant (p = 0.57).</p> <p>The median number of years since last MMR dose in the control group was 11 years (range 0–39).</p> <p>Median interval between disease onset and last MMR vaccine dose for index-case patients was 3 years.</p>		
Levine H, Rishpon S, Huerta-Hartal M, Davidovitch N. 2011. Preventing mumps outbreaks in confined settings: Comprehensive ring vaccination as a containment strategy. Hum Vaccin, 7(12): 1389-93.	MMR2, MMR3; Jeryl Lynn strain	Epidemiological report	<ul style="list-style-type: none"> • <u>Outbreak location</u>: Israel • <u>Duration of outbreak</u>: throughout 2005 (not defined) and September 2009 - August 2010 • <u>Population at risk</u>: Israel Defence Forces • <u>Intervention group</u>: soldiers in affected military units • <u>Other</u>: genotype G5 isolated from samples in both outbreaks 	<p>During the two waves of the 2005 outbreak, over 1,000 soldiers were immunized within one week of index case-report. In the first wave, all individuals were vaccinated with an additional MMR dose. In the second wave, individuals who received MMR2 were excluded. In both events, no further cases were found on active surveillance.</p> <p>During the 2009/10 outbreak, overall nearly 2,000 soldiers were vaccinated with an additional dose, independent of MMR vaccine status (>40 different events). Mumps infections only occurred within a single incubation period after the initiation of the vaccination campaign.</p>	II-3	Poor
Nelson GE, Aguon A, Valencia E, Oliva R, Guerrero ML, Reyes R, Lizama A, Diras D, Mathew A, Camacho EJ, Monforte MN, Chen TH, Mahamud A, Kutty PK, Hickman C, Bellini WJ, Seward JF, Gallagher K, Fiebelkorn AP. Epidemiology of a mumps	MMR3; Jeryl Lynn strain	Cohort	<ul style="list-style-type: none"> • <u>Outbreak location</u>: US (Guam) • <u>Duration of outbreak</u>: December 1, 2009- December 31, 2010 • <u>Population at risk</u>: 180,000 island residents • <u>Size of outbreak</u>: 505 cases; median age, 12 years • <u>Time of intervention</u>: May 18 - 21, 2010 • <u>Intervention group</u>: 9-14 year-old students with MMR2 	<p>Out of 3,364 eligible students 9-14 years old, 33% (n=1,068) received MMR3.</p> <p>Attack rates in eligible schools according to MMR3 status*:</p> <ul style="list-style-type: none"> - received MMR3: 0.09% - not received MMR3: 0.23% <p>*difference between groups (RR=0.4 [95%CI: 0.05-3.5]) was not statistically significant (p=0.67).</p>	II-2	Poor

<p>outbreak in a highly vaccinated island population and use of a third dose of measles-mumps-rubella vaccine for outbreak control - Guam 2009 to 2010. <i>Pediatr Infect Dis J.</i> 2013;32(4):374-80.</p>			<ul style="list-style-type: none"> • <u>Intervention setting</u>: 7 schools (from a total of 64 schools in Guam) with an attack rate >5/1,000 • <u>Other</u>: genotype G identified as an outbreak strain; peak of outbreak occurred one month prior to intervention. 	<p>Out of six students who were diagnosed with mumps in the post-intervention period, only one received MMR3.</p> <p>Incremental VE (MMR3 vs. MMR2): 61% (95% CI, -250 -95%) 21 or more days after vaccination</p>		
<p>Ogbuanu IU, Kutty PK, Hudson JM, Blog D, Abedi GR, Goodell S, Lawler J, McLean HQ, Pollock L, Rausch-Phung E, Schulte C, Valure B, Armstrong GL, Gallagher K. 2012. Impact of a third dose of measles-mumps-rubella vaccine on a mumps outbreak. <i>Pediatrics</i>, 130(6): e1567-74.</p>	<p>MMR1, MMR2, MMR3; Jeryl Lynn strain</p>	<p>Cohort</p>	<ul style="list-style-type: none"> • <u>Outbreak location</u>: US (NY state, Orange County) • <u>Duration of outbreak</u>: September 1, 2009 - June 30, 2010 • <u>Population at risk</u>: 20,300 religious community members • <u>Size of outbreak</u>: 790 cases in the community (72% 11-17 years of age) • <u>Intervention setting</u>: school (3 of 4 schools in the village attended by 98% of village school children) • <u>Time of intervention</u>: January 19 - February 2, 2010 • <u>Intervention group</u>: 11-17 year-old students • <u>Other</u>: household size in the affected community above average (5.7 versus the US national average of 2.6); peak of outbreak occurred in Nov/Dec 2009. 	<p>Out of 2,688 students 11-17 years of age, 1,723 received MMR3; a small number of students (n=87) received a catch-up dose of MMR1 or MMR2.</p> <p>Attack rates in students 11-17 years of age:</p> <ul style="list-style-type: none"> - 21 days prior to intervention: 4.93% - 21 days following intervention: 1.55% - 22-42 days following intervention: 0.13% <p>Incremental VE (MMR3 vs. MMR2): 88% (95% CI: -31.9%, 98.9%); broad CI intervals due to high rate of vaccine uptake and small number of cases >21 days post intervention (2 among the 413 unvaccinated students and 1 among the 1,723 vaccinated students)</p> <p>Decline in the mumps attack rate in the community post intervention was also statistically significant in the 11-17 year-old (96%; 95%CI: 87-99) and 5-10 year-old (72.9%; 95%CI: 52-84) age groups.</p>	<p>II-2</p>	<p>Fair</p>
<p>Salmón-Mulanovich G, Utz G, Lescano AG, Bentzel DE, Blazes DL. 2009. Rapid response to a case of mumps: implications for preventing</p>	<p>MMR1; Jeryl Lynn strain</p>	<p>Case series</p>	<ul style="list-style-type: none"> • <u>Outbreak location</u>: US Naval Medical Research Center Detachment in Lima, Peru • <u>Size of outbreak</u>: 1 case (index case) • <u>Intervention setting</u>: medical research facility 	<p>Out of 81 exposed employees, 8 were found to be vaccine and disease naïve based on history of infection and antibody titre of <20.0 U/ml.</p>	<p>II-3</p>	<p>Fair</p>

transmission at a medical research facility. Salud Publica Mex, 51(1): 34-8.			<ul style="list-style-type: none"> • <u>Intervention group</u>: mumps virus naive employees (i.e., without disease or vaccination history and with undetectable antibody titre) 	All eligible individuals received MMR vaccine within one week of exposure. No secondary cases of mumps were observed after the intervention.		
Veneti L, Borgen K, Borge KS, Danis K, Greve-Isdahl M, Konsmo K, Njølstad G, Nordbø SA, Øystese KS, Rykkvin R, Sagvik E, Riise ØR. 2018. Large outbreak of mumps virus genotype G among vaccinated students in Norway, 2015 to 2016. Euro Surveill. 2018;23(38):17006-42	MMR1, MMR2, MMR3; genotype A (Jeryl Lynn and RIT 4385)	Case series	<ul style="list-style-type: none"> • <u>Outbreak location</u>: Norway • <u>Duration of outbreak</u>: 6 September, 2015 - 30 June, 2016 • <u>Population at risk</u>: Whole population • <u>Size of outbreak</u>: 232 cases, median age 23 (>75% university students, 87% 19-28 years old) • <u>Time of intervention</u>: October 1-4 (Trondheim) and November 1-8 (Bergen), 2015 • <u>Intervention group</u>: under vaccinated students (vaccinated with MMR1 or MMR2) and close contacts of cases (vaccinated with MMR3) • <u>Other</u>: MMR schedule in Norway: dose provided at 15 months and 11-12 years of age; majority of tested samples (66/68) genotype G 	MMR3 provided to approximately 1,300 close contacts of cases, including household members. Only 3 cases, all within 2 weeks of vaccination, were reported among individuals who received MMR3.	II-3	Poor

APPENDIX B: SUMMARY OF SAFETY FINDINGS (ADVERSE EVENTS [AE] AND SERIOUS ADVERSE EVENTS [SAE])

Study Details					Summary	
Publication	Vaccine (dose provided), Strain	Study Design	Outbreak and study description	Summary of Key Findings	Level of Evidence	Quality
Aasheim E, Inns T, Trindall A, Emmett L, Brown K, Williams C, et al. Outbreaks of mumps in a school setting, United Kingdom, 2013. Hum Vaccin Immunother. 2014;10(8):2446-9	MMR1, MMR2, MMR3; Jeryl Lynn strain	Case series	N=76 students 10-19 years of age whose parents approved the administration of an additional MMR dose	No AEs were reported following vaccine administration.	II-3	Fair
<p>Abedi GR, Mutuc JD, Lawler J, Leroy ZC, Hudson JM, Blog DS, Schulte CR, Rausch-Phung E, Ogbuanu IU, Gallagher K, Kutty PK 2012. Adverse events following a third dose of measles, mumps, and rubella vaccine in a mumps outbreak. Vaccine, 30(49): 7052-8.</p> <p>Ogbuanu IU, Kutty PK, Hudson JM, Blog D, Abedi GR, Goodell S, Lawler J, McLean HQ, Pollock L, Rausch-Phung E, Schulte C, Valure B, Armstrong GL, Gallagher K. 2012. Impact</p>	MMR3; Jeryl Lynn strain	Case series	N= 1,597 students 11-17 years old	<p>Out of 1,755 students 11-17 years of age that received MMR3, 91% (1,597) returned for follow-up survey.</p> <p>AEs among survey respondents (student and parent reported):</p> <ul style="list-style-type: none"> - 7.2% (115) reported at least 1 local or systemic AE within 14 days of MMR3 administration; most commonly reported AEs were injection site pain, redness, or swelling (3.6%); joint or muscle aches (1.8%); dizziness or light-headedness (1.7%); and fever of 38 degrees Celsius or greater (1.3%). 0.2 % (3) reported fainting at any time during the 2-week period following vaccination. There were no significant differences in AE reported based on age and gender. -No SAEs were reported/identified in the 2 months following MMR3 vaccination either through the study survey, VAERS analysis (enhanced surveillance 	II-3	Fair

Study Details					Summary	
Publication	Vaccine (dose provided), Strain	Study Design	Outbreak and study description	Summary of Key Findings	Level of Evidence	Quality
Aasheim E, Inns T, Trindall A, Emmett L, Brown K, Williams C, et al. Outbreaks of mumps in a school setting, United Kingdom, 2013. Hum Vaccin Immunother. 2014;10(8):2446-9	MMR1, MMR2, MMR3; Jeryl Lynn strain	Case series	N=76 students 10-19 years of age whose parents approved the administration of an additional MMR dose	No AEs were reported following vaccine administration.	II-3	Fair
<p>Abedi GR, Mutuc JD, Lawler J, Leroy ZC, Hudson JM, Blog DS, Schulte CR, Rausch-Phung E, Ogbuanu IU, Gallagher K, Kutty PK 2012. Adverse events following a third dose of measles, mumps, and rubella vaccine in a mumps outbreak. Vaccine, 30(49): 7052-8.</p> <p>Ogbuanu IU, Kutty PK, Hudson JM, Blog D, Abedi GR, Goodell S, Lawler J, McLean HQ, Pollock L, Rausch-Phung E, Schulte C, Valure B, Armstrong GL, Gallagher K. 2012. Impact</p>	MMR3; Jeryl Lynn strain	Case series	N= 1,597 students 11-17 years old	<p>Out of 1,755 students 11-17 years of age that received MMR3, 91% (1,597) returned for follow-up survey.</p> <p>AEs among survey respondents (student and parent reported):</p> <ul style="list-style-type: none"> - 7.2% (115) reported at least 1 local or systemic AE within 14 days of MMR3 administration; most commonly reported AEs were injection site pain, redness, or swelling (3.6%); joint or muscle aches (1.8%); dizziness or light-headedness (1.7%); and fever of 38 degrees Celsius or greater (1.3%). 0.2 % (3) reported fainting at any time during the 2-week period following vaccination. There were no significant differences in AE reported based on age and gender. -No SAEs were reported/identified in the 2 months following MMR3 vaccination either through the study survey, VAERS analysis (enhanced surveillance 	II-3	Fair

of a third dose of measles-mumps-rubella vaccine on a mumps outbreak. Pediatrics, 130(6): e1567-74.				one year post intervention) or after contacting local primary health care providers. No differences were identified in the reporting of AE by grade or sex, for specific AE in the follow-up surveys.		
Albertson JP, Clegg WJ, Reid HD, Arbise BS, Pryde J, Vaid A, Thompson-Brown R, Echols F. Mumps outbreak at a university and recommendation for a third dose of measles-mumps-rubella vaccine- Illinois, 2015-2016. MMWR Morb Mortal Wkly Rep.. 2016;65(29):731- 4.	MMR1, MMR2, MMR3; Jeryl Lynn strain	Case series	N=>11,500 university students and staff born during or after 1957	No SAEs were reported following vaccine administration.	II-3	Fair
Levine H, Rishpon S, Huerta-Hartal M, Davidovitch N. 2011. Preventing mumps outbreaks in confined settings: Comprehensive ring vaccination as a containment strategy. Hum Vaccin, 7(12): 1389-93.	MMR2, MMR3; Jeryl Lynn strain	Epidemiological report	N=>2,000 soldiers	No AEs were reported following immunization.	II-3	Poor
Nelson GE, Aguon A, Valencia E, Oliva R, Guerrero ML, Reyes R, Lizama A, Diras D, Mathew A, Camacho EJ, Monforte MN, Chen TH, Mahamud A, Kutty PK, Hickman C, Bellini WJ, Seward JF, Gallagher K, Fiebelkorn AP. 2013. Epidemiology of	MMR3; Jeryl Lynn strain	Case series	N=533 children 9-14 years of age	AE data was collected through retrospective surveys. 6% (n=32) of students reported AEs in the 2 weeks following vaccination, with joint aches (2.6%), local pain/redness/swelling and dizziness (2.4%) being most common. No SAEs were reported.	II-3	Poor

<p>a mumps outbreak in a highly vaccinated island population and use of a third dose of measles-mumps-rubella vaccine for outbreak control - Guam 2009 to 2010. <i>Pediatr Infect Dis J.</i> 2013;32(4):374-80.</p>						
<p>Veneti L, Borgen K, Borge KS, Danis K, Greve-Isdahl M, Konsmo K, Njølstad G, Nordbø SA, Øystese KS, Rykkvin R, Sagvik E, Riise ØR. 2018. Large outbreak of mumps virus genotype G among vaccinated students in Norway, 2015 to 2016. <i>Euro Surveill.</i> 2018;23(38):1700642</p>	<p>MMR1, MMR2, MMR3; genotype A (Jeryl Lynn and RIT 4385)</p>	<p>Case series</p>	<p>N≈1,300 adults</p>	<p>No SAEs were reported.</p>	<p>II-3</p>	<p>Fair</p>