

An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI) †

Update on Measles-Mumps-Rubella-Varicella Vaccine and Febrile Seizures

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PREAMBLE

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

Febrile seizures are reported in 2% to 5% of children between the ages of 3 months and 5 years, frequently associated with underlying viral infections, and may follow childhood immunizations. Febrile seizures that are generalized but short-lived (< 15 minutes), and that do not recur within 24 hours are generally considered benign. There is evidence that combination MMRV vaccine products including Priorix-Tetra[®] (GlaxoSmithKline [GSK] Inc.) and ProQuad[™] (Merck Canada Inc.) are associated with a small but real increased risk of febrile seizures in the 7 to 10 days following immunization with the first dose in infancy, as compared to MMR and varicella vaccines administered in separate injections.

2. Who

Infants age 12 to 47 months receiving their first dose of MMRV vaccines.

3. How

Infants aged 12 to 47 months *may* receive a first dose of MMR and Varicella vaccines separately or the combined MMRV formulation. This consideration will be jurisdiction-specific depending on provincial/territorial immunization recommendations.

4. Why

With evidence that combined MMRV vaccine products including Priorix-Tetra[®] and ProQuad[™] are associated with a small but real increased risk of febrile seizures following the first dose compared to separate injections, parents need to be counselled and, depending on provincial and territorial immunization programmes, offered a choice of vaccination strategy.

I. INTRODUCTION

MMR vaccines have been available in Canada since the 1970s, and univalent varicella vaccines since 1998. The availability of a combined MMRV vaccine has enabled vaccine providers to reduce the number of injections. In 2010, NACI published 2 statements, one on recommendations for MMRV⁽¹⁾ and one on 2-dose varicella vaccination⁽²⁾.

Studies have shown a small increased risk for febrile seizures after the first dose of measles, mumps, rubella (MMR) vaccines given within the first 2 years of age. This increased risk has not been observed following the administration of univalent varicella vaccines⁽³⁾. There is ongoing evidence, however, that combined MMRV vaccine products including Priorix-Tetra[®] (GlaxoSmithKline [GSK] Inc., authorized in 2007) and ProQuad[™] (Merck Canada Inc., authorized in 2012 in Canada and 2006 in the United States) are associated with a small increase in the risk of febrile seizures in the 7 to 10 days following immunization when compared to MMR and varicella vaccines administered separately (MMR+V). At the time of publication of the MMRV statement in 2010, Priorix-Tetra[®] was the only product available in Canada and although there was evidence of an increased risk of fever following MMRV compared to MMR+V, there was not clear evidence that this increased risk of fever led to an increased risk in febrile seizures.

This statement reviews updated evidence for febrile seizures following measles-mumps-rubella-varicella (MMRV) vaccines, including new information related to Priorix-Tetra[®] and additional data on ProQuad[™], and provides recommendations for immunization programs.

II. ADVERSE EVENTS FOLLOWING MMRV AND MMR+V

Local reactions and fever after Priorix-Tetra[®]

As highlighted in the 2010 statement, data from published studies and from the manufacturer's database of over 6,700 administered doses have demonstrated the safety of combined MMRV vaccine (as Priorix-Tetra[®]). When it was given as a single dose to children after their first birthday, minor adverse events including fever were comparable to the MMR+V or MMR groups⁽⁴⁾.

In other studies, when two primary doses of MMRV (Priorix-Tetra[®]) were administered six to eight weeks apart after 12 months of age, the first dose was associated with a higher proportion of minor adverse events; i.e., pain in 8% to 12%, redness in 30%, swelling in 10%, fever in 60% to 68% (10% \geq 39.5°C), and measles/rubella-like or varicella-like rashes in 3% to 5%⁽⁵⁾⁽⁶⁾. These rates were comparable to the group given MMR+V, except for fever, which was significantly higher in the MMRV group, at 50% overall; however the proportion of children with fever \geq 39.5°C was similar in both groups. Proportions of adverse events were similar after the second dose of MMRV; pain in 9% to 14%, redness in 33%, swelling in 14%. However, fever was seen less often, in 36% to 43% (5% \geq 39.5°C), as well as a lower incidence of measles/rubella-like rash at 1%. Czaika et al. reported similar findings⁽⁷⁾, with fever following MMRV and MMR+V of 61% and 46% respectively.

Halperin et al.⁽⁸⁾ studied the use of these vaccines administered to infants aged 15 to 75 months who had previously received one dose of each of MMR+V after their first birthday. Children who had received their subsequent dose as MMRV, reported redness, local swelling and fever not

significantly different from the group that received MMR+V as the subsequent dose, except for pain, which was lower in the MMR+V group (24% vs 33%). A similar observation was made by Vesikari et al.: pain was reported by 73% of children in the group receiving a second-dose of MMRV (after a previous dose of MMRV) compared to 58% in children receiving a first dose of MMRV (after a previous dose MMR), though this finding was not statistically significant⁽⁹⁾. Fever was also not significantly different between the two groups (33% vs 22%). The number of children studied, however, was small (48 receiving the first dose as MMRV and 45 receiving MMR).

When MMRV was administered at least six weeks after MMR in 15 to 23 month-old and 2 to 6 year-old children in a study by Gillet et al.⁽¹⁰⁾, proportions of children reporting a generalized rash, varicella-like rash, measles or rubella-like rash, local pain and swelling were comparable to the corresponding control subgroup who received MMR+V, while local site redness was significantly more common in the MMRV group (28% vs 12%). However, fever $\geq 38.0^{\circ}\text{C}$ occurring within 14 days post-vaccination was more common in the MMRV subgroup (41%), than in the MMR+V subgroup (32%) in the children aged 15 to 23 months, but not in children aged 2 to 6 years. However, the risk of Grade 3 fever (i.e., $\geq 39.5^{\circ}\text{C}$) post-vaccination was not significantly different between study and control groups (2% to 3% each).

In a study in which MMRV was administered simultaneously with DTaP-HBV-IPV/Hib⁽¹¹⁾, the rate of localized redness, swelling and rash at the MMRV and DTaP-HBV-IPV/Hib injection sites was comparable to those in the single (individual) vaccine groups. The risk of fever in the simultaneous administration group was comparable to the MMRV only group (76% versus 74% respectively), which both were higher than the DTaP-HBV-IPV/Hib only group (48%), suggesting that MMRV was more likely to be responsible for the fever in the simultaneous administration group.

In summary, as a result of the pre-licensure observations of increased risk of fever with the administration of Priorix-Tetra[®] – in comparison to MMR and Varicella vaccines given separately – febrile seizures became a subject of particular post-marketing surveillance interest and studies were initiated to better understand this risk.

Recent studies of febrile seizures after MMRV vaccination

Febrile seizures are reported in 2% to 5% of children between the ages of 6 and 60 months⁽¹²⁾. They are frequently associated with underlying viral infections and may follow childhood immunizations. Simple febrile seizures are generalized, short-lived (< 15 minutes) and do not recur within 24 hours. They are generally considered benign, with an excellent neurological prognosis. A simple febrile seizure occurring after immunization is not considered a contraindication for future vaccination with either the same, or other childhood vaccines^{(13)(p77)}.

Febrile seizures after MMRV vaccination were initially reported in the U.S.A⁽¹⁴⁾: children receiving a first dose of ProQuad[™] had higher rates of febrile seizure when compared with children receiving MMR and varicella vaccines administered separately. In a post-licensure study by Klein and colleagues⁽¹⁵⁾ using the Vaccine Safety Datalink with 83,107 children aged 12 to 23 months who received MMRV vaccine and 376,354 children who received MMR and varicella (MMR+V) vaccines separately, the febrile seizure rate 7 to 10 days after vaccination was 9.3 per 10,000 vaccinations among the MMRV recipients and 4.6 per 10,000 vaccinations among the MMR+V recipients (adjusted odds ratio = 2.04; 95% CI: 1.44–2.90; $p < 0.0001$). It was estimated that one additional febrile seizure would occur for every 2,300 children immunized

with MMRV rather than with MMR+V. Of the 166 children who experienced febrile seizures after vaccination, 26 (16%) were hospitalized.

In a separate post-marketing study by Jacobsen et al.⁽¹⁶⁾ involving 14,263 children aged 12 to 60 months (99% were aged 12 to 23 months) in each group, the investigators reported a 2.3 times (95% CI: 0.6–9.0) higher relative risk (RR) for febrile seizures 5 to 12 days after MMRV vaccination (5 per 10,000 vaccinations), when compared with the historic control group of children vaccinated with MMR+V at the same visit (2 per 10,000 vaccinations). This study was later expanded to encompass a larger sample size, 31,298 children for each group, with similar results. The rate of febrile seizures 5 to 12 days after first vaccination with MMRV was 7/10,000 doses, as compared with 3.2/10,000 doses in the MMR+V group (RR = 2.2, 95% CI: 1.04–4.65). In February 2008, the USA's Advisory Committee on Immunization Practices (ACIP) changed its recommendations⁽¹⁷⁾ made in 2007, and rescinded their preference for the use of the combination MMRV vaccine over separate injections of MMR vaccine and varicella vaccine⁽¹⁷⁾. As indicated in their update, this change was a result of the preliminary data available but also as a result of limited availability of MMRV at that time.

In 2009, final data became available from the two post-licensure studies⁽⁴⁾⁽⁸⁾. In addition, while the incidence of febrile seizures after a second dose of ProQuad™ administered at 4 to 6 years of age in the U.S. was not initially assessed, the completed post-licensure studies were able to examine this question. For a second dose of MMRV (administered at 4-6 years of age), there was no increased risk of febrile seizures compared to MMR+V. A second dose of MMRV administered to children aged 15-26 months was also associated with lower risk of fever compared to a first dose of either MMRV or MMR+V, suggesting that the additional risk with MMRV is restricted to the first dose, regardless of age at second dose.

In 2010, the ACIP therefore updated its recommendations⁽¹⁸⁾ which included a multi-pronged approach. It advised that, for the first dose at age 12-47 months, either MMRV or MMR+V may be used, but further advised providers who would consider the administration of MMRV to discuss clearly the benefits and risks of both MMRV and MMR+V with parents. Unless the parent or caregiver expresses a preference for MMRV, MMR+V is preferred for the first dose in this age group. For the second dose, at any age, and for the first dose at age four and above, MMRV was preferred. Finally, ACIP also included an added precaution that children with a personal or familial history (sibling or parent) of seizures of any etiology, should receive separate MMR+V.

Febrile Seizures after Priorix-Tetra®

At the time of the change in ACIP's recommendations in 2010 and the publication of NACI's statements, the risk of febrile seizures after the administration of GSK's MMRV vaccine, Priorix-Tetra®, had not been reported to be higher when compared with MMR+V. This finding is in spite of the observed higher risk of fever $\geq 38.0^{\circ}\text{C}$ (although not for $\geq 39.5^{\circ}\text{C}$) after the first dose of MMRV in children under 2 years of age. It was unclear whether the less common occurrence of febrile seizure could be attributed to the lower potency of varicella present in Priorix-Tetra® compared with ProQuad™, or whether studies of Priorix-Tetra® had been too small to detect a true difference in febrile seizures. In a study by Schuster et al. in Germany⁽⁵⁾, in which two doses of MMRV, or MMRV followed by MMR, were administered six weeks apart in children 10 to 21 months of age, febrile seizure was uncommon and comparable in both MMRV and MMR+V groups. In the MMRV group, three out of 732 (0.4%) febrile seizures occurred (though only one of the three was deemed to be related to vaccination), while in the MMR+V group, there was one febrile seizure out of 232 [0.4%]. Gillet et al.⁽¹⁰⁾ also documented febrile seizures occurring

in their cohort of 458 children aged 15 months to 6 years previously vaccinated with MMR, and randomized to receive either MMRV or MMR+V, followed by a dose of varicella vaccine six to eight weeks later. Only one patient in the control group had febrile seizures, after both the administration of concomitant MMR+V vaccines and the second dose of varicella vaccine. Consequently, larger post-licensure studies were needed to determine if there was any increase in risk of febrile seizure after Priorix-Tetra®.

Using data on immunization and medical visits between 2006 and 2013, MacDonald et al.⁽¹⁹⁾ conducted a large population-based cohort study in Alberta of 277,774 children aged 12-23 months. They compared the risk of febrile seizures after the first dose of MMRV vaccine with MMR+V given separately during the same clinic visit. The study used two time periods: before the introduction of MMRV, from 2006 to mid-2010 (when MMR and varicella vaccines were given separately) and in the years following MMRV introduction, from mid-2010 to 2012. For each vaccine, an observational window was defined as 42 days prior to and 42 days following the vaccination visit, with a maximal risk window defined as between 7-10 days after immunization when viral replication would be highest and thus the risk of a febrile seizure the greatest. Age and calendar year were controlled. An elevated risk for MMRV vs. MMR+V was found only during the maximal risk window and was 1.99 (95% CI 1.30-3.05). This finding translated to an excess risk of 1 febrile seizure for every 2,841 doses of MMRV, consistent with the findings in the US with ProQuad™ and the first statistically significant finding for Priorix-Tetra®.

The study also looked at a sub-group of children at higher risk for seizures as a result of underlying medical conditions including a history of febrile seizures, seizure disorder or other neurologic conditions. Among those children, which represented 4% of the cohort (n=11,006) there was no difference between the two vaccination strategies (RR = 1.30, 95% CI 0.60-2.79). The differential risk between MMRV and MMR+V was not increased, which differed from what was found for the entire cohort or the low-risk subgroup (RR = 2.27, 95%CI 1.48-3.49).

III. RECOMMENDATIONS

Since the publication of the statements by NACI on MMRV and 2-dose varicella vaccination in 2010, evidence has accumulated of an increased risk of febrile seizures after the first dose of MMRV given up to 47 months of age, as compared to MMR and varicella given separately, for both products now available for use in Canada. This risk is estimated at about 1 additional febrile seizure for every 2,300 to 2,800 doses of MMRV vaccine. Studies suggest that the risk of febrile seizures is not elevated with a first dose given at age 4 years and older.

Recommendation #1:

For the first dose given up to 47 months of age, MMR and varicella vaccines can be given either as MMRV or MMR+V. However, the following considerations should be taken into account: parental acceptability of the increased risk of febrile seizure, potential impact on the perception of safety and vaccination coverage, as well as the need for an additional injection. These considerations may be jurisdiction-specific. (*NACI recommendation – Grade A*)

Recommendation #2:

Children at higher risk for seizures as a result of underlying medical conditions including a history of febrile seizures, seizure disorder or other neurologic conditions may receive MMRV.

(NACI recommendation – Grade B)

IV. RESEARCH PRIORITIES

Research to address the following outstanding questions is encouraged:

1. To refine post-marketing surveillance to determine the febrile seizure rates after MMRV or MMR+V vaccination in Canada.
2. To determine parental and provider preferences for single vaccine (MMRV) versus multiple injection vaccines (MMR+V) considering the differential risk of febrile seizures, and any impact on vaccination coverage.

TABLE

Table. NACI Recommendation for Immunization -- Grades

A	NACI concludes that there is good evidence to recommend immunization.
B	NACI concludes that there is fair evidence to recommend immunization.
C	NACI concludes that the existing evidence is conflicting and does not allow making a recommendation for or against immunization; however other factors may influence decision-making.
D	NACI concludes that there is fair evidence to recommend against immunization.
E	NACI concludes that there is good evidence to recommend against immunization.
I	NACI concludes that there is insufficient evidence (in either quantity and/or quality) to make a recommendation, however other factors may influence decision-making.

LIST OF ABBREVIATIONS

<i>Abbreviation</i>	<i>Term</i>
ACIP	Advisory Committee on Immunization Practices
GACVS	Global Advisory Committee on Vaccine Safety
GSK	GlaxoSmithKline
MMR	Measles-mumps-rubella
MMRV	Measles-Mumps-Rubella-Varicella vaccines
NACI	National Advisory Committee on Immunization
RR	Relative Risk

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Former NACI Members: Dr. D. Kumar, Dr. B. Seifert

Liaison Representatives: Dr. J. Blake (Society of Obstetricians and Gynaecologists of Canada), Dr. J. Brophy (Canadian Association for Immunization Research and Evaluation), Dr. A. Cohn (Centers for Disease Control and Prevention), Dr. J. Emili (College of Family Physicians of Canada), Dr. M. Lavoie (Council of Chief Medical Officers of Health), Dr. C. Mah (Canadian Public Health Association), Dr. D. Moore (Canadian Paediatric Society), Dr. A. Pham-Huy (Association of Medical Microbiology and Infectious Disease Canada), Ms. E. Sartison (Canadian Immunization Committee).

Ex-Officio Representatives: Dr. (LCdr) K. Barnes (National Defence and the Canadian Armed Forces), Ms. G. Charos (Centre for Immunization and Respiratory Infectious Diseases [CIRID], Public Health Agency of Canada [PHAC]), Dr. G. Coleman (Biologics and Genetic Therapies Directorate, Health Canada [HC]), Dr. J. Gallivan (Marketed Health Products Directorate [MHPD], HC), Ms. J. Pennock (CIRID, PHAC), Dr. T. Wong (First Nations and Inuit Health Branch [FNIHB], HC).

Former Ex-Officio Representatives: Dr. J. Brooks (CIRID, PHAC), Dr. (LCol) P. Eagan (National Defence and the Canadian Armed Forces), Dr. B. Law (CIRID, PHAC), Ms. M. St-Laurent (CIRID, PHAC).

†This statement was prepared by Dr. R. Pless, Dr. C. Quach and approved by NACI.

REFERENCES

- (1) National Advisory Committee on Immunization (NACI). Statement on Measles-Mumps-Rubella-Varicella Vaccine. *Can Commun Dis Rep.* 2010;36(ACS-9):1-22.
- (2) National Advisory Committee on Immunization. Varicella vaccine 2-dose recommendations for children aged 12 months to 12 years in Canada. *Can Commun Dis Rep.* 2009.
- (3) Macartney KK, Gidding HF, Trinh L, et al. Febrile seizures following measles and varicella vaccines in young children in Australia. *Vaccine.* 2015;33(11):1412-7.
- (4) Nolan T, McIntyre P, Robertson D, et al. Reactogenicity and immunogenicity of a live attenuated tetravalent measles-mumps-rubella-varicella (MMRV) vaccine. *Vaccine.* 2002;21(0264-410; 3-4):281-9.
- (5) Schuster V, Otto W, Maurer L, et al. Immunogenicity and safety assessments after one and two doses of a refrigerator-stable tetravalent measles-mumps-rubella-varicella vaccine in healthy children during the second year of life. *Pediatr Infect Dis J.* 2008;27(0891-3668; 8):724-30.
- (6) Knuf M, Habermehl P, Zepp F, et al. Immunogenicity and safety of two doses of tetravalent measles-mumps-rubella-varicella vaccine in healthy children. *Pediatr Infect Dis J.* 2006;25(0891-3668; 1):12-8.
- (7) Czajka H, Schuster V, Zepp F, et al. A combined measles, mumps, rubella and varicella vaccine (Priorix-Tetra): Immunogenicity and safety profile. *Vaccine.* 2009;27(47):6504-11.
- (8) Halperin SA, Ferrera G, Scheifele D, et al. Safety and immunogenicity of a measles-mumps-rubella-varicella vaccine given as a second dose in children up to six years of age. *Vaccine.* 2009;27(0264-410; 20):2701-6.
- (9) Vesikari T, Baer M, Willems P. Immunogenicity and Safety of a Second Dose of Measles-Mumps-Rubella-Varicella Vaccine in Healthy Children Aged 5 to 6 Years. *Pediatr Infect Dis J.* 2007;26(0891-3668; 2):153-8.
- (10) Gillet Y, Steri GC, Behre U, et al. Immunogenicity and safety of measles-mumps-rubella-varicella (MMRV) vaccine followed by one dose of varicella vaccine in children aged 15 months-2 years or 2-6 years primed with measles-mumps-rubella (MMR) vaccine. *Vaccine.* 2009;27(0264-410; 3):446-53.
- (11) Zepp F, Behre U, Kindler K, et al. Immunogenicity and safety of a tetravalent measles-mumps-rubella-varicella vaccine co-administered with a booster dose of a combined diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-Haemophilus influenzae type b conjugate vaccine in healthy children aged 12-23 months. *Eur J Pediatr.* 2007;166(0340-6199; 8):857-64.
- (12) Febrile Seizures: Guideline for the Neurodiagnostic Evaluation of the Child With a Simple Febrile Seizure | From the American Academy of Pediatrics | Pediatrics Available at: <http://pediatrics.aappublications.org/content/127/2/389>. Accessed 12/18/2015, 2015.

- (13) National Advisory Committee on Immunization. Canadian Immunization Guide 2006. : Public Health Agency of Canada; 2006.
- (14) Advisory Committee on Immunization Practices. Update: recommendations from the Advisory Committee on Immunization Practices (ACIP) regarding administration of combination MMRV vaccine. MMWR Morb Mortal Wkly Rep. 2008;57(1545-861; 10):258-60.
- (15) Klein NP, Fireman B, Yih WK, et al. Measles-Mumps-Rubella-Varicella Combination Vaccine and the Risk of Febrile Seizures Pediatrics. 2010; 2010;126(1):e1 <last_page> e8.
- (16) Jacobsen SJ, Ackerson BK, Sy LS, et al. Observational safety study of febrile convulsion following first dose MMRV vaccination in a managed care setting. Vaccine. 2009;27(1873-2518; 34):4656-61.
- (17) Marin M, Guris D, Chaves SS, et al. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm.Rep. 2007;56(1545-8601; -4):1-40.
- (18) Marin M, Broder KR, Temte JL, et al. Use of combination measles, mumps, rubella, and varicella vaccine recommendations of the advisory committee on immunization practices (ACIP). Morb Mortal Wkly Rep. 2010;59(RR-3):1-12.
- (19) MacDonald SE, Dover DC, Simmonds KA, et al. Risk of febrile seizures after first dose of measles-mumps-rubella- varicella vaccine: A population-based cohort study. CMAJ. 2014;186(11):824-9.