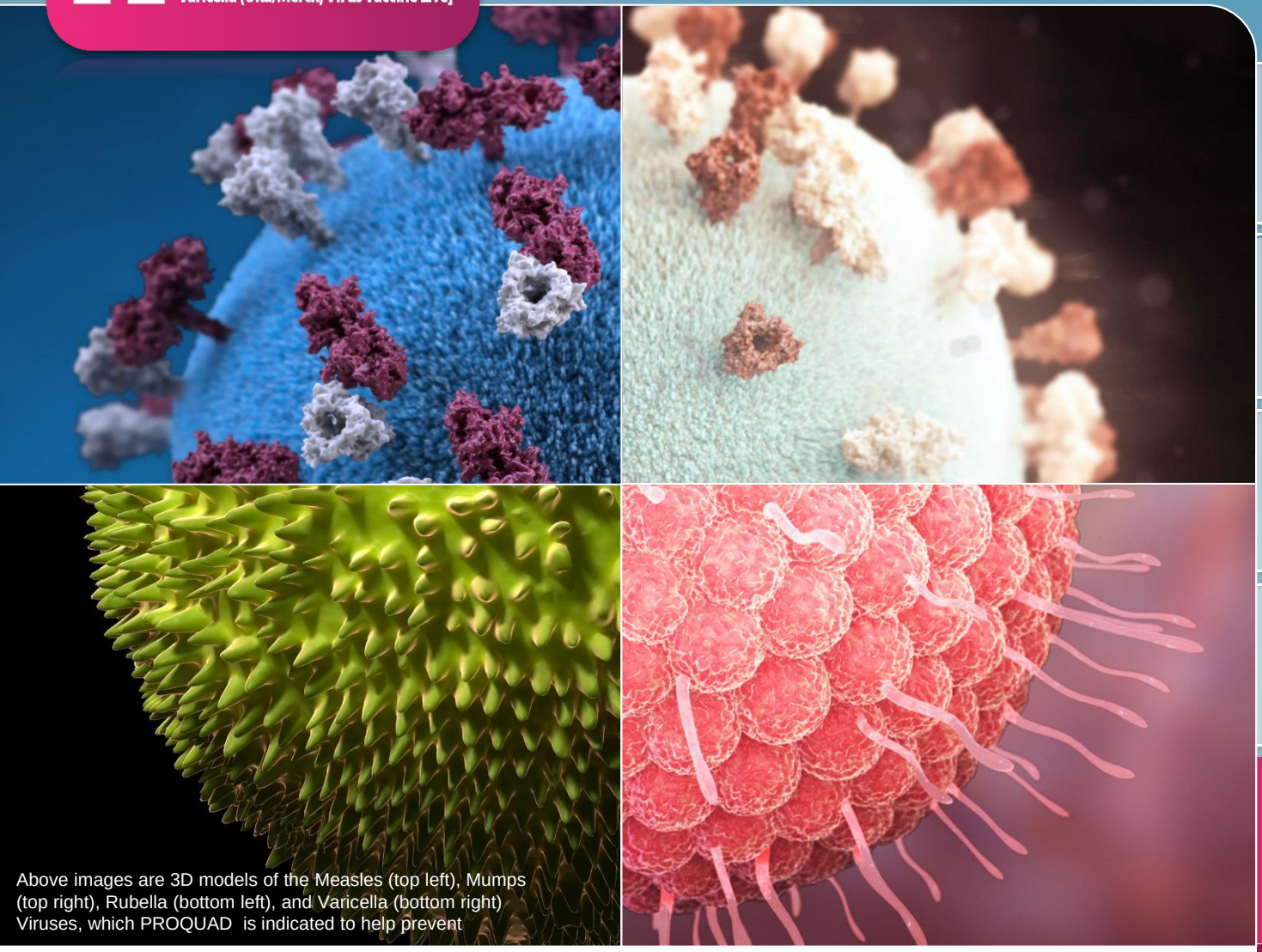
ProQuad™
[Measles, Mumps, Rubella and Varicella (Oka/Merck) Virus Vaccine Live]

ISSUE RESPONSE GUIDE



Above images are 3D models of the Measles (top left), Mumps (top right), Rubella (bottom left), and Varicella (bottom right) Viruses, which PROQUAD is indicated to help prevent

Select a category to view

RESPONDING TO UNSOLICITED QUESTIONS

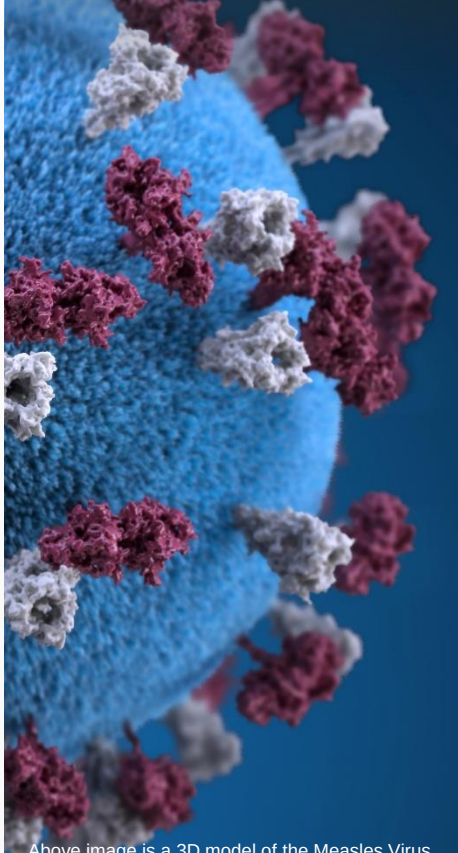
HOME

When responding to a question, make sure that you first understand it and then provide the appropriate information.

The CRCT format – which stands for Clarify, Respond, Confirm, Transition – will help you to respond appropriately to a customer's question.

CLARIFY	If you are not sure what the customer wants to know, ask an open question. If you think that you understand the question, verify your understanding by paraphrasing it in a closed question.
RESPOND	If you know the answer, respond to the question by providing the appropriate information. If you do not know the answer, inform the customer that you will obtain the answer for them.
CONFIRM	Confirm that you have addressed the issue to the customer's satisfaction.
TRANSITION	Transition back to the discussion using approved resources.

Appropriate safety information must be provided as part of each balanced discussion with customers.



Above image is a 3D model of the Measles Virus, one of the four viruses for which PROQUAD is indicated to help prevent

QUESTION 1

How should ProQuad be incorporated into the pediatric vaccination schedule?

CLARIFY	Doctor, at what age do you currently initiate vaccination against measles, mumps, rubella, and varicella for your patients?
RESPOND	The use of MMRV (ProQuad) vaccine can vary from country to country. ProQuad is indicated for vaccination against measles, mumps, rubella, and varicella in individuals 12 months through 12 years of age. The Ministry of Health (MoH) may decide what fits best with your country's clinical needs. For example currently, the United States, Australia, Canada, and Israel have national immunization programs that include MMRV. When used as a first dose, ProQuad is associated with a higher relative risk of febrile seizures at 5 to 12 days after vaccination compared with M-M-RII and VARIVAX administered concomitantly. In a postmarketing observational surveillance study, results from the primary safety analysis revealed an approximate two-fold increase in the risk of febrile seizures in the same 5- to 12-day time frame after vaccination with the first dose of ProQuad. The incidence of febrile seizures 5 to 12 days after dose 1 of ProQuad (0.70 per 1000 children) was higher than that in children receiving M-M-RII and VARIVAX concomitantly (0.32 per 1000 children) with a relative risk (RR) of 2.20. (95% CI: 1.04, 4.65) Moreover, this postmarketing study reported no cases of febrile seizures during the 5-to 12-day postvaccination time period among 26,455 children who received ProQuad as a second dose of M-M-R II and/or VARIVAX. An Australian study published by Macartney et al in 2017 evaluated the effect of earlier (age 18 months) scheduling of MMRV vaccine as the second dose of measles-containing vaccine (MCV) on safety and coverage. In the primary analysis which adjusted for age using 3 age groups between 11 and 23 months, there was no significantly increased risk of febrile seizures within the 5- to 12-day risk period following MMRV, the prevaccination period, or the 13- to 30-day postvaccination period. It is important to note that this is not necessarily the vaccination schedule followed in all countries.
CONFIRM	Does that help you determine how to incorporate ProQuad into your current pediatric vaccination schedule, doctor?
TRANSITION	Doctor, let's turn now to safety. In clinical trials involving children 12 to 23 months of age, ProQuad was generally well tolerated…

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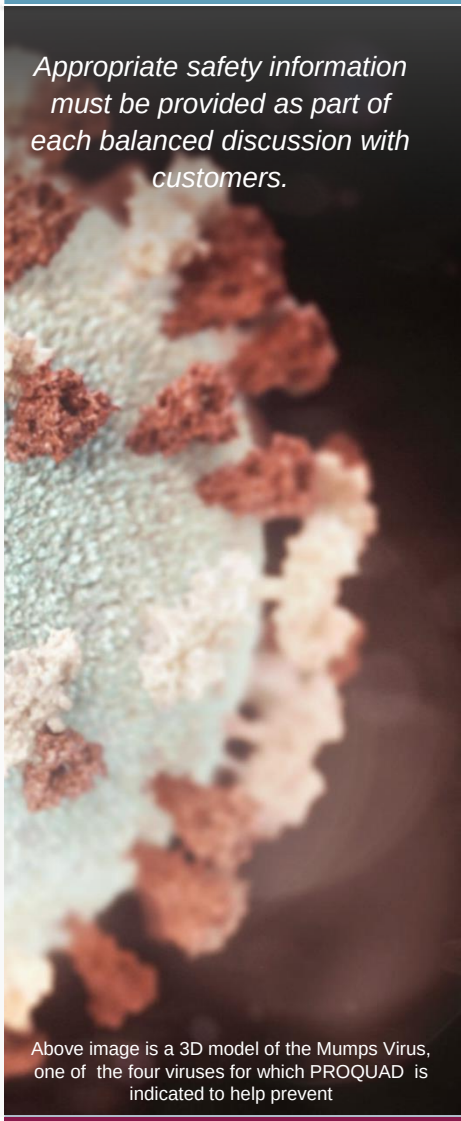

Above image is a 3D model of the Mumps Virus, one of the four viruses for which PROQUAD is indicated to help prevent

QUESTION 2

What are the advantages of choosing an MMRV combination vaccine over using separate varicella and MMR vaccines?

CLARIFY	Doctor, share with me the criteria you consider when selecting the measles, mumps, rubella, and varicella vaccines you currently administer to your pediatric patients. Do you take into account a combination MMRV vaccine as an option?
RESPOND	The advantages of combination vaccines include fewer injections for children, facilitation of vaccine delivery, and a potential decrease in the number of physician/clinic visits. Combination vaccines have shown significant time savings for activities associated with vaccine preparation, vaccine injection, and administrative duties, as well as reduction of infant crying time, and have been shown to reduce costs associated with parental perceptions of pain and emotional distress. In addition, combination vaccines have the potential to increase coverage rates through the simultaneous administration of multiple antigens at one visit. Both the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (AAP) have indicated that combination vaccines are generally preferred over monovalent vaccines or concomitant administration of monovalent vaccines at different injection sites on the same day.
CONFIRM	Doctor, does ProQuad meet your criteria for selecting a more convenient vaccine for your appropriate patients?
TRANSITION	Doctor, let's talk about how ProQuad may fit into your vaccination schedule.

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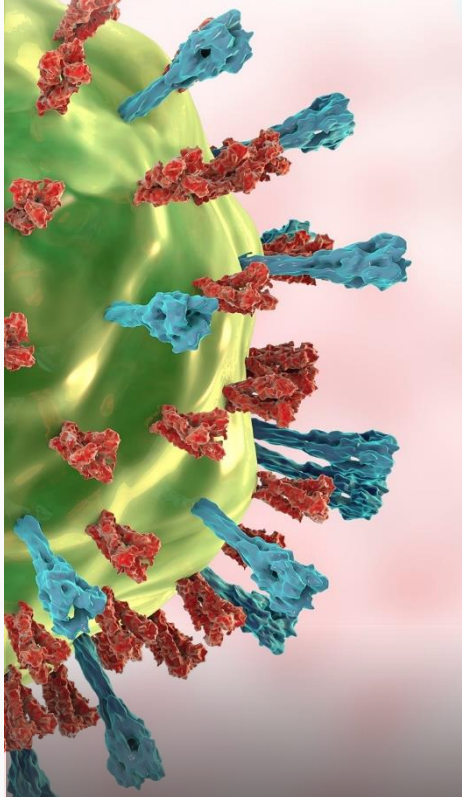

Above image is a 3D model of the Mumps Virus, one of the four viruses for which PROQUAD is indicated to help prevent

QUESTION 3

What efficacy data is available for ProQuad?

CLARIFY	Doctor, are you familiar with the efficacy data on the components of ProQuad – VARIVAX and M-M- R II?
RESPOND	Formal studies to evaluate the efficacy of ProQuad have not been published. However, the efficacy of the measles, mumps, and rubella components (M-M-R II) and varicella components (VARIVAX) of ProQuad have been demonstrated in numerous studies. More than 518 million doses of M-M-R II have been distributed worldwide (1978 to 2007). Widespread use of a 2-dose vaccination schedule in the United States and countries such as Finland and Sweden has led to a >99% reduction in the incidence of each of the 3 targeted diseases. Vaccination against measles, mumps, and rubella has led to a significant reduction in the incidence of these diseases. In combined clinical trials of VARIVAX, the protective efficacy of the vaccine against all forms of varicella ranged from 81 to 100%. In a large case-control study, the vaccine was estimated to be 85% effective against all forms of varicella and 97% effective against moderately severe and severe disease. Long-term estimated efficacy for the vaccine against all forms of varicella over 10 years was 94%. Antibody responses against varicella virus ≥5 units/mL in the glycoprotein enzyme-linked immunosorbent assay (gpELISA, a highly sensitive assay which is not commercially available) have been shown to be highly correlated with long-term protection. Clinical studies have shown that vaccination with ProQuad elicits rates of antibody responses against varicella virus ≥5 units/mL in the gpELISA similar to those observed after vaccination with VARIVAX. According to the CDC, in the US, annual morbidity rates due to varicella have declined 96% as of 2013, as compared to the pre-vaccine era.
CONFIRM	Doctor, does that answer your question?
TRANSITION	Doctor, let's discuss the dosing recommendations for ProQuad.

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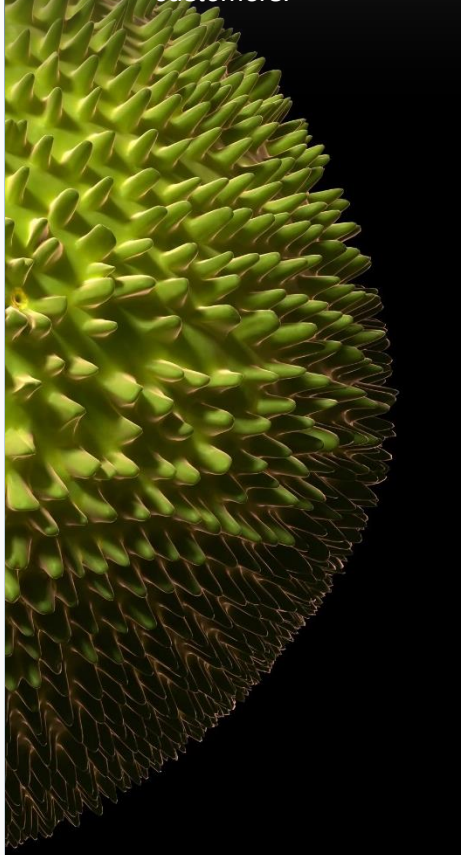

Above image is a 3D model of the Rubella Virus, one of the four viruses for which PROQUAD is indicated to help prevent

QUESTION 4

What data do you have on the refrigerated formulation compared to the frozen formulation of ProQuad?

CLARIFY	Doctor, are you asking about the differences between the refrigerated and frozen formulations of ProQuad?
RESPOND	A study conducted in the US (2002-2003) demonstrated that the immunogenicity and the safety of a refrigerator-stable formulation of ProQuad are similar to the previously licensed frozen formulation. A total of 1519 healthy children, 12 to 23 months of age, were vaccinated with either the refrigerator-stable formulation (n = 1006) or the frozen formulation (n = 513) of ProQuad. No vaccine-related serious adverse experiences were reported within the follow-up period. The overall rate of serious adverse experiences between recipients of the refrigerated and frozen formulations of ProQuad was not statistically significant (0.7% and 0.4%, respectively). All serious adverse experiences were medical conditions that are generally expected of a pediatric population. For both the refrigerator-stable and frozen formulations of ProQuad, the response rate was ≥97.7% for measles, mumps, and rubella, and the percentage of patients with a varicella zoster virus antibody titer of ≥5 gpELISA U/mL after vaccination was ≥88.8%. The response rates to each vaccine antigen in patients who received the refrigerator-stable formulation of ProQuad were considered similar to those in the frozen formulation.
CONFIRM	Does that answer your question regarding the differences between the refrigerated and frozen formulations, Doctor?
TRANSITION	Doctor, let's discuss what your patients and parents can expect in terms of safety and tolerability with ProQuad.

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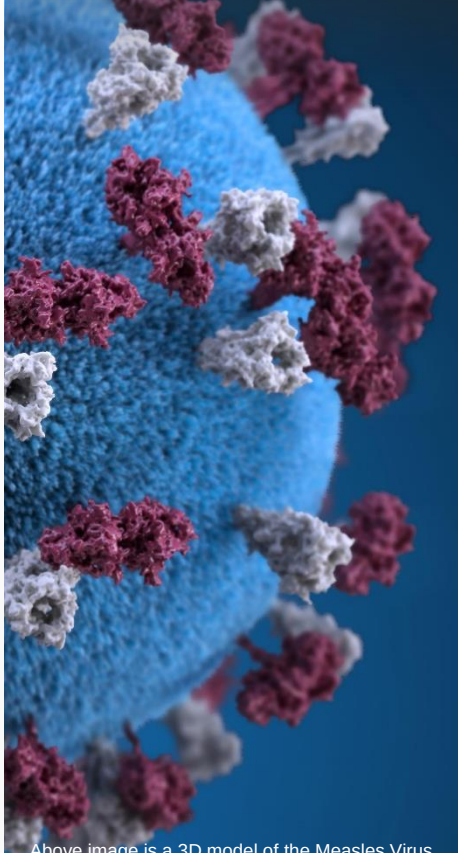

Above image is a 3D model of the Measles Virus, one of the four viruses for which PROQUAD is indicated to help prevent

QUESTION 5

How do ProQuad and Priorix-Tetra® compare?

CLARIFY	Doctor, are you currently administering Priorix-Tetra to your patients?
RESPOND	While ProQuad and Priorix-Tetra are both indicated for vaccination against measles, mumps, rubella, and varicella, there are significant differences in immunogenicity. In a multicenter, observer-blind phase 2 study, 1,783 healthy 12- to 14-month old infants were randomized to receive either refrigerator-stored Priorix-Tetra, freezer-stored Priorix-Tetra, or freezer-stored ProQuad, concomitantly with hepatitis A vaccine (Havrix) and 7-valent pneumococcal conjugate vaccine (Prevnar). Seroresponse rates and antibody geometric mean concentrations/titers were determined by ELISA and neutralization assays. Noninferiority of both formulations of Priorix-Tetra vaccines versus ProQuad was demonstrated for seroresponse rates at Day 42 to measles, mumps, and rubella viruses. However, neither formulation of Priorix-Tetra fully demonstrated comparable immunogenicity to ProQuad for the varicella-zoster virus component. Seroresponse rates for refrigerator-stored and freezer-stored Priorix-Tetra were 57.1% and 69.8% respectively, while the seroresponse rate for ProQuad was 86.7%. Geometric mean concentration ratios for anti-varicella-zoster virus demonstrated noninferiority (lower 97.5% confidence interval ≥0.5) versus ProQuad for the freezer-stored formulation of Priorix-Tetra only.
CONFIRM	Are there any other questions I can answer regarding ProQuad?
TRANSITION	Doctor, let's talk about what your patients and parents can expect in terms of safety and tolerability with ProQuad.

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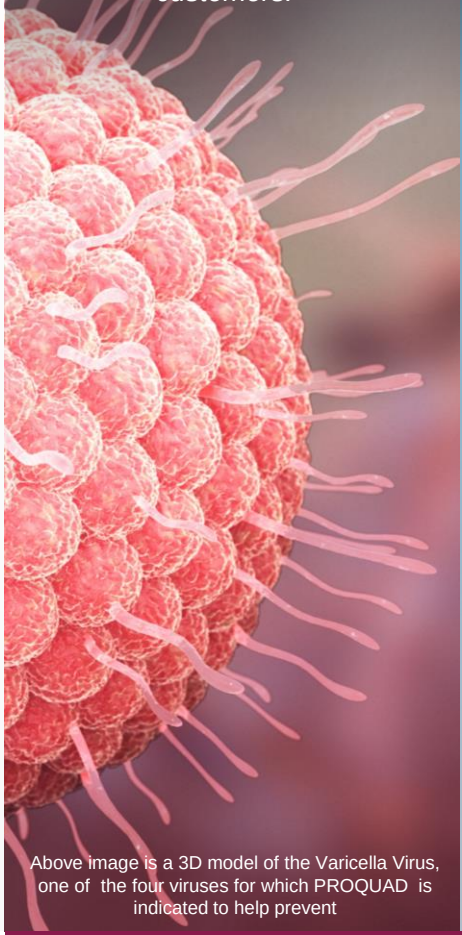

Above image is a 3D model of the Varicella Virus, one of the four viruses for which PROQUAD is indicated to help prevent