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Using Disease Epidemiology to Optimize Immunization Schedules

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Macartney et al¹ report in this issue of *JAMA Pediatrics* on the safety of using combination measles-mumps-rubella-varicella (MMRV) vaccine as the second dose of measles-mumps-rubella (MMR) vaccine and sole dose of varicella vaccine in Australia, and the effect of this policy on national vaccine coverage. They found that there was no increase in febrile seizures when MMRV is administered in the second year of life approximately 6 months after a first dose of MMR and that on-time vaccination increased with use of MMRV. Are these findings an indication that the timing and use of combination MMRV vaccine should be reconsidered for the United States?

In the United States, since measles vaccine was first recommended in 1963, the measles vaccination schedule changed as knowledge of measles immunity increased and the epidemiology of measles evolved. An analysis of measles outbreaks occurring from 1985 to 1986 showed that outbreaks in which preschoolers predominated were largely related to failure to receive any doses of vaccine. In contrast, in outbreaks that affected primarily school-aged children, the major problem was 1-dose vaccine failure.^{2,3} In 1989, because of measles outbreaks among school-aged children, the US Advisory Committee on Immunization Practices (ACIP) recommended 2 doses, with the first dose at age 15 months and the second dose at age 4 through 6 years, before school entry. Because of the success of the measles vaccination program in achieving and maintaining high 1-dose MMR vaccine coverage in preschool-aged children and high 2-dose MMR vaccine coverage in school-aged children, measles was verified as eliminated from the United States in 2000.⁴

Varicella vaccine (Varivax; Merck & Co Inc) was recommended for all children aged 12 to 18 months in 1995, following which the number of cases and rate of annual varicella-associated hospitalizations declined in the United States. Hospitalization rates decreased 100% among infants, and substantial declines also were recorded in all other age groups.⁵ However, despite high 1-dose vaccination coverage, outbreaks continued to occur. A second dose of varicella vaccine was recommended at age 4 to 6 years, harmonized with the recommendation for MMR vaccine use. The recommended age for the second dose was supported by the epidemiology of varicella, with a low incidence among preschool-aged

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children and higher incidence and more outbreaks among elementary-school-aged children.⁵ With the second dose recommended, varicella declined still further. Between 2005–2006 (before the 2-dose recommendation) and 2013–2014, the overall varicella incidence declined 84.6%, with the largest declines reported in children aged 5 to 9 years (89.3%) and 10 to 14 years (84.8%).⁶

In 2005, a combined live, attenuated MMRV vaccine (Pro-Quad; Merck & Co Inc) was licensed for use in children aged 12 months to 12 years. The use of combination vaccines is a practical way to reduce the number of injections a child receives and can improve timely vaccination coverage; combination vaccines also have the advantages of (1) reducing the cost of stocking and administering separate vaccines, (2) reducing the cost for extra health care visits, and (3) facilitating the addition of new vaccines into immunization programs.⁷ Because combination vaccines are generally preferred when indicated, the ACIP recommended that 1 dose of MMRV vaccine be administered on or after the first birthday as the first dose of these antigens. However, in 2008, the ACIP was informed of evidence of an increased risk of febrile seizures after administration of the combination MMRV vaccine compared with separate MMR and varicella vaccines.⁸ An excess risk of febrile seizures of 4.3 per 10 000 after MMRV vaccine administration compared with separate MMR plus varicella vaccination was observed.⁹ Based on these findings, in 2009, the ACIP recommended that, for the first dose of measles, mumps, rubella, and varicella vaccines at age 12 to 47 months, either MMR vaccine and varicella vaccine or MMRV vaccine may be used, but that MMR vaccine and varicella vaccine should be generally administered rather than MMRV.¹⁰ The second dose of MMRV vaccine has been found to be less likely to cause fever than the first dose (when administered to children aged 12 to 23 months 90 days after the first dose).¹¹ For the second dose of measles, mumps, rubella, and varicella vaccines at any age (15 months to 12 years) and if the first dose is given at 48 months or older, the ACIP expressed a preference for use of MMRV vaccine over separate injections of MMR vaccine and varicella vaccine.¹⁰

Macartney et al¹ report that data from the national Australian Childhood Immunisation Register in 2012 showed that vaccine uptake was suboptimal; approximately 92% of children had received 2 measles-containing vaccines by age 5 years and modeling indicated an increased risk of measles outbreaks. A single dose of monovalent varicella vaccine, scheduled at age 18 months, had coverage of only 86% by age 2 years (although increasing to 92% by 5 years).

In the United States, varicella vaccine coverage for 1 or more doses among children aged 19 to 35 months reached 90% in 2006 and has remained above 90% for 1 or more doses since then.¹² All 50 US states and Washington, DC, require at least 1 dose of varicella vaccine for kindergarten entry; 42 states and Washington, DC, require 2 doses.¹³ During the 2015–2016 school year, median vaccination coverage (determined using estimates from the 50 states and Washington, DC) was 94.6% for 2 doses of MMR vaccine and 94.3% for 2 doses of varicella vaccine. Twenty-two states reported that coverage exceeded 95%.¹³

The Australia experience confirms the value of using combination vaccines and administering vaccines when children are already visiting their physicians. Good

immunization policy requires such careful evaluation of the epidemiology of disease and the existing program platforms. In the United States, the epidemiology of measles—the most contagious of the 4 vaccine-preventable diseases in the MMRV vaccine—indicated that the herd immunity threshold to stop transmission in preschool children was substantially lower than for school-aged children.¹⁴ In the context of a successful US immunization program with high 2-dose coverage, elimination of measles, control of varicella, and a growing concern that waning of mumps vaccine-induced immunity may be contributing to recent mumps outbreaks in the United States (<https://www.cdc.gov/mumps/outbreaks.html>), the ACIP has not considered a change to an earlier second dose of MMR and varicella vaccines indicated for the United States. However, countries with different epidemiologic patterns, where 1-dose vaccine failure for any of the antigens in MMRV is a problem in preschool children or the extra injection plays a role in decreasing coverage, may consider administering the second dose of MMRV earlier.¹⁵ The key is the principle of using the epidemiology of disease to determine the appropriate immunization schedules for any country.

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