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Long-term protection against varicella with two-dose combination measles-mumps-rubella-varicella vaccine

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In 2014, WHO estimated that approximately 4·2 million severe complications leading to hospital admission and 4200 related deaths occur globally each year because of varicella (also known as chickenpox).[1] By comparison with other vaccine-preventable diseases in childhood, such as measles and diphtheria, mortality and morbidity from varicella are lower.[2] However, the frequency of infection and indirect costs such as from parents taking time off from work, mean varicella has a substantial, albeit underestimated, economic impact.[2] Varicella monovalent vaccines first became widely available in the mid to late 1990s. By the mid-2000s two new vaccines that combined varicella and measles-mumps-rubella (MMR) were licensed on the basis of non-inferior immunogenicity of the constituent components to the separate vaccines. However, despite the potential for these four-in-one MMRV vaccines to simplify immunisation programme schedules and improve varicella vaccine uptake,[3] by 2015 only an estimated 31 countries had adopted routine universally funded varicella vaccination, with either MMRV or monovalent varicella vaccines.[2]

In 2014, the first randomised (phase 3a) trial of a two-dose short course of MMRV vaccine against varicella in children aged 12–22 months, from ten varicella-endemic European countries, followed up over a 3-year period was published.[4] In *The Lancet Infectious Diseases*, Michael Povey and colleagues[5] report results from the phase 3b extension of this study with a total median follow-up time of 9·8 years. Vaccine efficacy was assessed in three groups of children who, 42 days apart, received two doses of measles-mumps-rubella-varicella (MMRV) vaccine (Priorix Tetra, GSK; per-protocol cohort at study end, n=2279), MMR vaccine (Priorix, GSK) followed by monovalent varicella vaccine (Varilrix, GSK; n=2266), or two doses of MMR vaccine as the control group (n=744). Vaccine efficacy against all varicella was 95·4% (95% CI 94·0–96·4) in children who received two doses of MMRV, and 67·2% (62·3–71·5) for MMR vaccine followed by varicella vaccine (MMR+V). For moderate or severe varicella, vaccine efficacy was notably higher, at 99·1% (97·9–99·6) for MMRV, and 89·5% (86·1–92·1) for MMR+V.

Over the near 10-year study period, varicella was reported in 76 (3%) children in the MMRV group, 469 (21%) in the MMR+V group, and 352 (47%) in the MMR control group, providing strong evidence of the endemic circulation of varicella-zoster virus in the participating countries in the absence of widespread vaccination. A decline in vaccine efficacy over time was not evident. Estimates at the 10-year follow-up were similar to those at 3 years, and annual vaccine efficacy was stable at more than 91·4% for the MMRV group and more than 59·4% for MMR+V group. The vaccines also had a good safety profile over years 3–10, with no difference in proportions of patients with serious adverse

events between the three groups and none deemed to be vaccine related. As seen for this and the other licensed MMRV vaccine, compared with MMR vaccine (with or without varicella vaccine), fever is two-times more likely occur in the 5–12 days after vaccination following dose one in children aged 12–24 months,[4-6] and has been associated with a higher proportion of children with febrile seizures.[6,7] An increased risk of febrile seizures after MMRV vaccine is given as the second dose of measles-containing vaccine has not been observed.[3]

A strength of the study is the long-term follow-up, which is unusual for vaccine trials, given vaccination of participants in the control group often occurs over time. However, a limitation of the study was the reduction in participants available for follow-up; only 3791 (65%) of the total vaccinated cohort were in the per-protocol cohort for efficacy at study end. In addition, geometric mean concentrations of antibody to varicella-zoster virus increased over the 10-year follow-up in participants, including those who received MMR vaccine only (418 of 2989 the immune persistence cohort), of whom 73% were varicella-zoster virus seropositive by year 10 but only 47% reported having varicella. This suggests the possibility of underascertainment of varicella cases, a high rate of subclinical infection or very mild disease, or a combination of these factors.

The low vaccine efficacy (67·2%, 95% CI 62·3–71·5) of single-dose monovalent varicella vaccine against all varicella was noteworthy. This finding is consistent with the pooled single-dose varicella vaccine effectiveness estimate for the same vaccine from ten observational studies in a recent meta-analysis of 77% (95% CI 62–85).[8] Protection against moderate to severe disease was greater in the study by Povey and colleagues[5] and the meta-analysis (89·5% and 98%, respectively).[5,8] For countries that have adopted using a single dose of MMRV vaccine, such as Australia,[3] the question of whether the MMRV vaccine would do better than single dose monovalent vaccine, remains unanswered. The varicella-zoster virus content is the same in both vaccines, and varicella-zoster virus geometric mean concentrations obtained after vaccination are comparable.[9]

The short-term and long-term outcomes of this randomised trial[4,5] are compelling with respect to the superiority of two-dose over one-dose varicella vaccination schedule. Countries with a single-dose vaccination programme, or introducing varicella vaccination, need to ask: is protecting against severe varicella enough? Two doses of varicella-containing vaccine are required for optimal protection, reducing the risk of breakthrough cases and outbreaks. Limiting varicella-zoster virus transmission also means fewer primary infections and a reduced risk of varicella-zoster virus reactivation causing herpes zoster later in life or in the immunocompromised. For these and other countries who do not yet vaccinate against varicella, incorporating new combination vaccines must be cost-effective—in many settings more work is needed to show varicella disease burden[1] and thus, the potential economic effect of varicella-containing vaccine, which must be introduced with appropriately tailored pricing. Despite improvements in measles control over the past decade, measles cases increased 31% globally during 2016–17.[10] Although it is exciting to see the effect that new combination viral vaccines such as MMRV can have, ensuring that vaccine uptake against the most serious viral illnesses in children, such as measles and rubella, is uniformly high across the globe remains our greatest public health challenge.

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I declare no competing interests.

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