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Major Article

Incidence rate of breakthrough varicella observed in healthy children after 1 or 2 doses of varicella vaccine: Results from a meta-analysis

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Background: Although extensive varicella vaccination coverage has been reported in many countries, breakthrough varicella (BV) still occurs in healthy children. We performed a meta-analysis to understand whether 2 varicella vaccine doses are needed in children and, if so, to determine the best time to vaccinate.

Methods: The BV incidence rates after 1 or 2 doses of varicella vaccine were pooled using random effects, and 95% confidence intervals (CI) were used to estimate the risk factors after vaccination.

Results: A total of 27 original articles were included in this meta-analysis. The pooled average BV incidence rate in children vaccinated with 1 dose was 8.5 cases per 1,000 person years (PY) (95% confidence interval [CI], 5.3-13.7; random effects model) and 2.2 cases per 1,000 PY (95% CI, 0.5-9.3; random effects model) in children vaccinated with 2 doses. The pooled trend of the annual BV incidence rate from the first to eighth year fluctuated, with a peak annual incidence rate of 35.3 cases per 1,000 population in the fourth year. The meta-regression showed that design type, type of vaccine, and their interaction accounted for approximately 71.74% of the heterogeneity in the average BV incidence rate after 1 vaccine dose.

Conclusions: Two doses of varicella vaccine are more effective than a single dose, and 3-4 years between the first and second vaccinations may achieve higher efficacy.

BACKGROUND

Varicella is an acute, highly contagious disease caused by the varicella zoster virus, which occurs primarily in unvaccinated children aged 1-14 years.[1] Although varicella is self-limiting with generalized pruritic vesicular rash mild disease in children, it can result in serious morbidity and mortality, especially in neonates, those with chronic comorbid conditions, and immunocompromised people.[2] In 1974, the live, attenuated varicella vaccine was developed in Japan and then used commercially in 1987. Many clinical trials involving the varicella vaccine have confirmed that it is well tolerated and effective in preventing varicella in healthy children.[3-5] A recent meta-analysis found that the 1-dose and 2-dose vaccine effectiveness against all varicella strains was 81% and 92%, respectively.[6]

The Oka-Merck varicella vaccine was first implemented as a universal routine vaccination in 1995 for children aged >12 months in the United States, and the incidence rate decreased from 10.3 cases per 1,000 population to 1.1 during the first 10 years.[7] The age-adjusted mortality rate decreased from 0.41 per million population in 1990-1994 to 0.05 in 2005-2007.[8] Furthermore, varicella-associated hospitalizations and outpatient visits declined by 93% (from 2.35 cases per 100,000 population to 0.16) and 84% (from 215 cases per 100,000 population to 33), respectively, when compared with the prevaccination period.[9] A drastic reduction in hospitalizations, incidence, and varicella-related deaths were also found in other countries after universal routine vaccination implementation.[10,11] However, herpes zoster or shingles incidence increased from 3.2 cases per 1,000 population in 1997 to 4.5 in 2012.[12]

Although high vaccination coverage was reported, varicella outbreaks still occurred.[13,14] Varicella which occurred >42 days after vaccination after exposure to wild-type virus was called

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breakthrough varicella (BV).[15] In clinical trials, BV symptoms included <50 skin atypical lesions, no fever, fewer complications, and milder symptoms than seen in unvaccinated cases.[15] Children who failed to seroconvert after vaccination or who lost antibody during follow-up years may be at risk for BV.[16] The average BV incidence rate varied from 2.09 cases per 1,000 person years (PY)[17] to 21.7.[18] Considering the increasing trend in BV incidence and relatively high number of BV cases, the Advisory Committee on Immunization Practices in the United States recommended a routine 2 doses of varicella vaccine in 2006.[15] However, breakthrough cases were still observed even after the 2 doses of varicella vaccine were given; the average BV incidence rate was up to 17.9 cases per 1,000 PY.[19] The reported annual BV incidence rates were different, increasing significantly from 1.6 cases per 1,000 PY within the first year to 9.0 at 5 years and 58 at 9 years after 1 dose of vaccine.[20] Another article also found that the annual BV incidence rates increased from 0.04% in 2008 to 0.32% in 2013 after 1 dose of vaccine.[21] However, another article reported that the annual BV incidence rates were stable within 4 years and then deceased after 1 dose of vaccine.[22]

The aim of our study was to investigate the average BV incidence rate worldwide, the importance of 2 doses of varicella vaccine, and the optimal time for the second vaccination, by pooling the average and annual BV incidence rates for 1 or 2 doses of varicella vaccine.

METHODS

This article followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Search strategy

We searched PubMed, Embase, and Web of Science and China National Knowledge Infrastructure (http://www.cnki.net) up to September 30, 2016, using the following terms: "varicella" OR "chickenpox" OR "varicella zoster virus" AND "vaccination" OR "vaccine" AND "breakthrough" OR "BV" without language restriction. The title and abstract of each article was reviewed to select relevant publications by 2 independent authors, and the full text was searched by relevant journal(s) or Google Scholar (http://scholar.google.com/). Additional publications in personal reference lists from original research articles were also reviewed. For missing or unpublished data, we tried to contact the corresponding authors by e-mail.

Selection criteria

Two reviewers independently applied the inclusion criteria for assessment of eligibility for meta-analysis, and the disagreements between reviewers were resolved by other authors. Articles were included if they met several criteria: (1) children were healthy children and had no varicella before vaccination, (2) children received varicella vaccination (1 or 2 doses), (3) participants were followed-up >42 days after vaccination, and (4) breakthrough cases and sample size data were available. When multiple publications from the same population resource or overlapping data sets were available, only the most recent, larger, or most informative study was included in this meta-analysis.

Data extraction

For each of the eligible studies, the first author's name, year of publication, study design, country, mean or median age at time of vaccination, follow-up time, dose and type of vaccine, sample size, and BV cases were extracted by 2 independent reviewers using a structured pilot form.

Quality assessment

According to the selection criteria, studies with an unvaccinated control group was not necessary; therefore, selection of the nonexposed cohort and comparability from the Newcastle-Ottawa scale were excluded, and only selection criteria and outcome assessment were included. Therefore, the quality scores of the studies ranged from 0-6 based on quality criteria fulfillment.[23] Two reviewers independently evaluated the included studies, and any discrepancy was resolved through discussion until a consensus was reached.

Statistical analysis

A metafor package of the R (version 3.3, Statistics Department of the University of Auckland) software was used for this meta-analysis. The metaprop function was used to pool the incidence rate if data were formatted by numbers of breakthrough cases and numbers of vaccinated population, or the metarate function was used if data were provided by PY. Because of the existence of extreme values, pooled estimate was calculated after log10 transformation for individual studies to stabilize the variance.[24] The I^2 value ≤50% was used to assess significance between study heterogeneity. The fixed effects model (the Mantel-Haenszel method) was used if no significant heterogeneity was found; otherwise, the random effects models (the DerSimonian and Laird methods) were used instead. If there was a higher heterogeneity between studies, a sensitivity analysis and subgroup analysis were used to evaluate whether ≥1 studies significantly affected the pooled results. Finally, a metareg function was used to assess the impact of ≥1 covariates. Publication bias was investigated visually using funnel plots and statistically using quantitative Begg and Egger tests. If publication bias existed, the trim and fill method was then used to produce an adjusted pooled effect and 95% confidence interval (CI).[25]

RESULTS

Search results

The search strategy yielded 260 relevant, nonduplicated publications. Forty-one original studies met our inclusion criteria after reviewing the title and abstract. For primary analysis, we restricted the analysis to trials published in full text. Two articles, which covered the same population, were both included because one of the articles described the average BV incidence rate[18] and another contained information about the annual BV incidence rate.[26] One study included 4 birth cohorts (2007-2010), and each birth cohort had a different follow-up duration with different BV incidence rates.[21] Finally, a total of 27 original articles containing 27,642 breakthrough cases were included in this meta-analysis (Fig 1). The basic characteristics of the 27 articles are presented in Table 1.

Average BV incidence rate after 1 dose of varicella vaccine

Twenty-five articles involving 30 study populations were included, and a total of 27,618 breakthrough cases were found during the follow-up period from 11 months-14 years. The pooled 1-dose average BV incidence rate for children was 8.5 cases per 1,000 PY (95% CI, 5.3-13.7; $I^2 = 99.8\%$, random effects model) and is shown in Figure 2 and Table 2.