REVIEW ARTICLE

Varicella: Efficacy of Two-Dose Vaccination in Childhood

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SUMMARY

Introduction: Experience with one-dose varicella vaccination of children in the USA has shown that with high immunization coverage a marked decline in morbidity and mortality occurs. However, about one quarter of the vaccinees may develop breakthrough varicella. Although breakthrough infections are usually mild, the patients are potentially contagious.

Methods: Selective literature search, review of congress papers, and evaluation of the consensus statement of an expert panel on the use of monovalent varicella vaccines.

Results: Recent studies on the causes, effects, and consequences of breakthrough varicella after one-dose vaccination show that varicella vaccine should be given in two doses at least four to six weeks apart to achieve effective, long-lasting protection against chickenpox. Breakthrough disease cannot always be prevented, but two-dose vaccination offers significantly better protection than a single dose. These findings were considered in the approval process for the measles-mumps-rubella-varicella combination vaccines, which are licensed only for use in a two-dose schedule.

Discussion: The authors recommend the general implementation of a two-dose schedule for single-antigen varicella vaccines, which will continue to be available.

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Key words: varicella, vaccination recommendation, prophylactic vaccination, immunization coverage, prevention

In July 2004, the Robert Koch Institute's Standing Vaccination Committee (Ständige Impfkommission, STIKO) made standard vaccination of all children and adolescents against varicella a part of its vaccination calendar (1). On the basis of the data from clinical studies that were available at that time, the STIKO recommended single-dose vaccination of children aged 1 to 13 years with the monovalent varicella vaccines that had been approved until then. Yet approval studies for new, combined vaccines with a varicella component, i.e., measles-mumps-rubella-varicella (MMRV) vaccines, require a two-dose schedule. To assist in the decision process regarding the possible future use of monovalent vaccines, a consensus conference of physicians and scientists from multiple disciplines was convened in Munich, Germany, in November 2007, on the initiative of the Paul Ehrlich Institute (2). In this article, we will summarize the scientific data underlying the position taken by the consensus conference regarding vaccination with monovalent vaccines.

The implementation of vaccination

Vaccination is recommended for the general population in order to achieve a marked reduction of the high morbidity due to varicella in Germany and of the associated complications, hospitalizations, and deaths, as well as the associated economic costs (3, 4, 5) (*table*). Furthermore, persons belonging to clinically relevant risk groups, such as patients suffering from leukemia or receiving intensive immunosuppressive therapy, will profit from the herd immunity that mass vaccination induces (i.e., even non-vaccinated individuals will be protected against the disease if the vaccination rate is high enough) (6).

Despite some initial resistance and slow assumption of the costs of vaccination by the statutory health insurance carriers in Germany, varicella vaccination met with broad acceptance among both physicians and the general public within one year of its introduction, and even more so after the combined MMRV vaccines became available. This is implied by data from the epidemiological surveillance program of the Robert Koch Institute's Measles/Varicella Working Group (Arbeitsgemeinschaft Masern/Varizellen) (7): the same number of initial varicella vaccinations (per sentinel physician and month) as initial measles vaccinations have been performed in

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TABLE

Varicella disease burden before the introduction of mass vaccination in Germany

Estimated number of cases of varicella in Germany, 1999 (4)	760 000
Estimates on the basis of a retrospective survey of doctors' practices for the year 1999 (3, 4)	Complicated disease course in 5.7% of patients
Findings of the German Pediatric Surveillance Unit (Erhebungseinheit für seltene pädiatrische Erkrankungen in Deutschland, ESPED), 2003 and 2004 (5)	Hospitalized cases of varicella in children under age 17: N = 918, mean age 3.3 years. 16% of patients had severe complications (secondary bacterial infection, coagulopathy, meningoencephalitis, cerebral infarction, and other complications) 10 deaths due to varicella 15 patients with permanent damage
Estimates based on ESPED data supplemented with data from other independent sources (5)	2640 children and adolescents under age 17 are treated in the hospital for varicella every year. Most of these patients do not belong to any risk group.
ICD-10 data from a small number of Statutory Health-Insurance Physicians' Associations, 2004* (personal communication)	Complications arise in 3.2% to 5.6% of all cases of varicella

* These data were kindly supplied by the Statutory Health-Insurance Physicians' Associations of Hamburg, Mecklenburg-West Pomerania, and Thuringia.

Germany since November 2006. Nonetheless, public acceptance remains a problem in some regions. A randomized poll of parents in Munich in late 2006, for example, revealed vaccination rates of 38% for varicella, but 86% for measles, among children aged 18 to 36 months (7).

The reporting physicians of the Measles/Varicella Working Group and the Bavarian Varicella Project (Bayerisches Varizellen-Projekt) have also documented an increasing rate of varicella breakthrough disease among vaccinated children, currently accounting for 3% to 5% of all cases of varicella (7).

Monovalent varicella vaccines

The antibody concentration is correlated with protection

The body's immune defense against varicella-zoster virus (VZV) is essentially based on cell-mediated immune responses that are still technically difficult to demonstrate. The immune response to the vaccine is therefore judged from the concentration of VZV-specific serum antibodies (8).

In early clinical studies, seroconversion was said to have taken place if anti-VZV antibodies were demonstrable four to six weeks after vaccination, regardless of the magnitude of the antibody titer. The seroconversion rate among children under the age of 13 years, when determined in this way, was 96% to 98% after a single dose of vaccine.

Clinical data indicate, however, that the magnitude of the primary humoral immune response four to six weeks after vaccination does indeed correlate with the rate of protection against varicella (9). When antibody titers were measured with the anti-VZV glycoprotein ELISA (gp-ELISA) test, it was found that the rate of breakthrough disease among children whose titers were 5 gp-ELISA units/mL or above was lower, by a factor of 3.5, than that of children whose titers were below this value (9).

The notion of seroconversion was therefore replaced by a determination of the percentage of vaccinated

children who had an antibody titer of 5 gp-ELISA units/mL or above six weeks after a single-dose vaccination. This arbitrarily defined "protective titer" was achieved by only 86% of the vaccinated children (9). A fluorescent antibody to membrane antigen (FAMA) test showed that a titer of 1:4 by this measure, obtained 16 weeks after vaccination, was also correlated with protection (10).

Long-term protection by vaccination

The results of longitudinal studies are hard to interpret, because one must assume that children continue to be exposed to wild virus that may contribute to the maintenance of protection against varicella through a sub-clinical booster effect.

Thus, it was first assumed, in accordance with study data, that vaccination in a single dose had a long-term protective effect, yet there are now an increasing number of reports that put this assumption in question. In the USA, varicella outbreaks continue to arise in schools and day-care centers despite a high vaccination rate. A regional surveillance program in the USA recently published an evaluation of data from the years 1995 through 2004 (11), revealing that 9.5% of vaccinated persons had breakthrough disease. Children aged 8 to 12 years who had been vaccinated with a single dose more than five years earlier had a significantly higher risk of developing varicella than children who had been vaccinated less than five years earlier (relative risk [RR], 2.6; 95% confidence interval [CI], 1.2–5.8). While older studies had shown a constant or slowly decreasing rate of breakthrough disease over time, this study showed a significant rise in the frequency of vaccination breakthrough, from 1.6 cases per 1000 person-years in the first year after vaccination to 6.9 in the fifth year and 9.0 in the ninth (11). At nearly the same time, a meta-analysis of reports on 14 varicella outbreaks that had been published from 1995 to 2006 concluded that the efficacy of one-dose vaccination is 72.5%.

The authors considered breakthrough disease to be caused by waning immunity after single-dose vaccination (12). Apparently, young age at the time of vaccination is a further risk factor for breakthrough disease, in addition to a long elapsed time since the vaccination (13).

Breakthrough varicella after single-dose vaccination

There is controversy over the question whether the increasing frequency of breakthrough disease with a longer elapsed time from vaccination might be due to inadequate "priming" by the vaccination, or whether it is because the immunity wanes over time.

Arvin and Gershon (8) postulate that an insufficient number of virus-specific memory T cells are generated after one-dose vaccination. According to their hypothesis, the immune memory response is less intense after a moderate initial stimulus than after a strong one, because the virus-specific effector cell populations are down-regulated within weeks or months after the primary contact with the antigen (8). In this view, the generally moderate course of breakthrough disease (*figure 1*) indicates that priming has indeed taken place after the single dose of vaccine, but that the initial stimulus did not suffice for complete protection. The fact that a second dose of vaccine brings about a stronger immune memory response supports this hypothesis, as a stronger response would not be expected if a robust primary immune response had already occurred. This means that varicella vaccines, unlike other live-virus

vaccines such as measles vaccine, exert their effects through a pronounced "prime-boost" mechanism (oral communication from M. Pfeleiderer, 102nd annual meeting of the German Society for Child and Adolescent Medicine [Deutsche Gesellschaft für Kinder- und Jugendmedizin], Mainz, 2006).

A two-dose vaccination schedule would provide additional protection to primary non-responders (ca. 5%) and also lessen the risk of breakthrough disease in immunized persons whose initial priming was inadequate. The obvious question arises whether a vaccine containing more virus than the currently approved vaccines would have as good an effect in a single dose as the latter have in two doses. The answer is likely to be no, because, as the quantity of antigen increases, a plateau effect comes about, so that the immune response probably cannot be made any stronger (14).

One- versus two-dose vaccination

The efficacy of a single dose versus two doses of vaccine was tested in a randomized clinical study involving 2216 children who were vaccinated in the USA from 1991 to 1993 (15). Over 10 years of follow-up, the cumulative rate of breakthrough disease in children who had been vaccinated twice was lower by a factor of 3.3 than that of children who had been vaccinated once (2.2% compared to 7.3%; $p < 0.001$). Breakthrough disease most commonly occurred two to five years after vaccination in both groups. Among the children who had been vaccinated twice, no breakthrough disease at

Figure 1: The difference in severity of varicella between unvaccinated and vaccinated children

a) Varicella in unvaccinated children – classic chickenpox: 200 to 500 cutaneous lesions. The clinical diagnosis is usually unequivocal. The skin lesions are mainly vesicular and appear in two to four grouped clusters. The patient has a high fever and feels ill. (From: Kreth HW: Varizellen. In: Wutzler P, Sauerbrei A (eds.): Varicella-Zoster-Virus-Infektionen: Aktuelle Therapie und Prophylaxe, 2nd edition, Bremen, Uni-Med Verlag AG 2007; 32–41, with the kind permission of the publisher.)

b) Varicella in immunized children – breakthrough illness among vaccine non-responders: fewer than 50 cutaneous lesions of atypical morphology, few or no vesicles, less contagious. Differential diagnosis: insect bites, allergic rash, Coxsackie virus infection, herpes simplex, impetigo

The frequency of vaccination reactions in healthy children aged 12 months to 12 years (mean age 4.4 years) after the administration of the first and second doses of a mono-valent varicella vaccine. Period of observation, 42 days. * Redness, swelling, pain on days 0–3 (from [21]).

all arose during the interval from seven to ten years after vaccination.

The children who had been vaccinated twice, three months apart, had significantly higher antibody titers six weeks after the second dose of vaccine (142.6 versus 12.5 gp-ELISA U/mL) than those in the comparison group, and nearly all of them reached or exceeded the critical antibody titer value of 5 gp-ELISA U/mL, which correlates with protection against varicella (99.6% versus 85.7%). That is, a two-dose vaccination schedule led to higher seroprotection rates (with antibody titers in the presumably protective range) as well as to higher geometric mean titer values.

A recently published study concerns a varicella outbreak among school and preschool children in Arkansas, USA, in 2006. 97% of them had been vaccinated against

varicella, and 41% had received two doses of vaccine (16). Of the 85 varicella cases that were registered, only 25 were among children who had been vaccinated twice. According to an estimate based on historical rates of disease transmission, the efficacy of the vaccine schedule was approximately 5% higher in a two-dose schedule than in a one-dose schedule (87% versus 81.8%).

In another study, in which a second dose of vaccine was given four to six years after the first one, the antibody concentration rose in most study participants, from a mean of 25.7 to a mean of 143.6 gp-ELISA U/mL (17). It thus seems to be unimportant, at least with respect to the antibody titer, whether the second dose is given just a few weeks after the first or, alternatively, only when the child is 4 to 6 years old (18).

The combined MMRV vaccines, when given in two doses, produce a comparable immune memory response against varicella to the response produced by the mono-valent varicella vaccines. In clinical studies, Shinefeld et al. (19) found a rise in the antibody concentration from 13 to 588 gp-ELISA U/mL six weeks after the second MMRV vaccination, and Knuf et al. (20) found a geometric mean anti-VZV antibody titer that was more than 20 times higher after the second dose of an MMRV vaccine. This pronounced booster effect of the second dose of vaccine has also been confirmed by other investigators (oral communication from V. Schuster and colleagues at the 24th annual meeting of the European Society for Paediatric Infectious Diseases, Basel, 2006).

No data are yet available on the efficacy of varicella vaccination in Germany since its introduction in 2004. Results from other countries cannot be automatically extrapolated to Germany, because efficacy data can be heavily influenced by vaccination rates, vaccination schedules, and sociodemographic factors of the population being immunized. Thus, a case-control study is currently being performed in the Munich area to investigate the efficacy of one- and two-dose vaccination with the nationally approved varicella vaccines, given in various different schedules (study director: PD Dr. Johannes Liese, Munich).

Rates of hospitalization due to varicella before and seven years after the introduction of childhood varicella vaccination in the USA (from [24]).

Varicella vaccines should be administered in a two-dose schedule

The booster effect of the second vaccine dose, which is otherwise atypical of live-attenuated vaccines, is a common feature of all of the varicella viruses that are currently approved for use in Germany and the European Union, regardless whether they are given in a mono-valent formulation or as a component of a combined MMRV vaccine (oral communication from M. Pflieger, 102nd annual meeting of the German Society for Child and Adolescent Medicine [Deutsche Gesellschaft für Kinder- und Jugendmedizin], Mainz, 2006). This special property of varicella vaccines was recognized and analyzed during the evaluation of the new MMRV fourfold vaccines. In the framework of the clinical studies that were performed for approval of these vaccines, two-dose vaccination schedules were also subjected to close clinical study for the first time. The same effect of the second dose of varicella vaccine was found in all

studies, for all products in all formulations, regardless of whether the varicella vaccine was given as a component of an MMRV vaccine or separately from an MMR vaccine (18, 19, 20).

The conclusion that can be drawn from all of these studies has to do with the inherent properties of the Oka-Varicella-Zoster virus vaccine strain. Over the course of attenuation by which the wild virus isolate was converted to the Oka vaccine, the immunogenic properties of the wild virus were apparently weakened. As a result, the balance between adequate immunogenicity (efficacy) and tolerability of the vaccine in a single dose was altered to the detriment of efficacy. This can be compensated for, however, by the booster effect of the second dose, as demonstrated by the rise in seroprotection rates and antibody titers. Thus, the second dose of a varicella vaccine should not be thought of as a secondary catch-up vaccination, but rather as the completion of the vaccination schedule.

Varicella vaccines are generally well tolerated in either one or two doses. Vaccination reactions are no more common or more severe after the second dose than after the first (except for local reactions), as shown by a study of healthy children aged 12 months to 12 years (*figure 2*) (21). No severe undesired events were observed. Rare allergic reactions have been described. There have also been a few reports of immediate allergic reactions, pneumonia, and the transmission of the virus in the vaccine to susceptible (usually immune-compromised) contact persons (22).

Experience with varicella vaccination strategies

The introduction of a varicella vaccination program in the USA in 1995 led to a marked decrease in morbidity and mortality due to chickenpox and lowered the associated costs for the American health-care system (23). The efficacy of vaccination in the USA, as determined mainly in studies of individual outbreaks of disease, ranged from 44% to 86%; a meta-analysis of 14 studies arrived at a figure of 72.5% (12).

Moreover, it has been shown that vaccination prevents more than 95% of all serious illnesses due to varicella, i.e., more than 95% of varicella cases that result in hospitalization (24) and death (25) (*figure 3*). Despite these achievements, however, there are still varicella outbreaks with transmission rates of 10% to 40%, usually in groups of children with a high vaccination rate (23). Breakthrough varicella usually takes a mild course, but patients are mainly contagious through their nasopharyngeal secretions. If the cutaneous lesions are relatively few and mild, it is difficult to diagnose chickenpox, recognize outbreaks promptly, and take the proper measures in response.

The American Advisory Committee on Immunization Practice accordingly changed its recommendations regarding varicella vaccination in August 2006 with the aim of improving the protection that vaccination provides (23). The original vaccination strategy, in which a single dose of varicella vaccine was recommended for children aged 12 months to 12 years and two doses spaced four to

BOX

A two-dose vaccination schedule improves protection against varicella*¹

- All children aged 11 to 23 months receive two doses of varicella vaccine:
a first dose usually at the age of 11 to 14 months,
a second dose usually at the age of 15 to 23 months.
The interval between the two doses should be no less than 4 to 6 weeks.
- Supplementation of vaccination with a second dose for all persons who have not yet reached their 18th birthday, who have not had varicella, and who have received only a single dose of vaccine to date (or none at all). If possible, this should be performed before the child begins school or group child care.
The interval between the two doses should be no less than 4 to 6 weeks.
- Post-exposure vaccination of all susceptible persons*² in varicella outbreaks.

*¹ Recommendations of an expert group (2).

*² Persons considered susceptible are those who were not vaccinated, or were vaccinated only once, and have no history of varicella (either clinically evident or laboratory-documented).

eight weeks apart were recommended for adolescents aged 13 years and older, was altered so that children should receive two doses as well. The first dose is to be given, as before, at the age of 12 to 15 months, and the second is to be given at the age of four to six years (this timing was chosen partly for compatibility with the recommendations for MMR vaccination).

Two-dose schedules for monovalent vaccines

Because recent studies have documented that varicella vaccines should be given twice at an interval of at least four to six weeks to assure effective and long-lasting protection against varicella, the expert group determined that the recommendations for vaccination with monovalent vaccines need to be changed accordingly (*box*). Breakthrough disease cannot be prevented in absolutely every case with a two-dose schedule, yet two doses protect much more effectively against varicella than one. These facts were taken into account during the approval procedure for the combined MMRV vaccines. The German Paul Ehrlich Institute reports that a change in the approval for monovalent vaccines can be expected in the near future, in which the administration of varicella vaccine to children in two doses will be approved for both monovalent and combination vaccines.

The above discussion of two-dose varicella vaccination is largely based on studies from the USA. In Germany, the second dose of vaccine should be administered during a child's second year of life, both because varicella is still highly prevalent among preschool children in Germany and so that the varicella vaccination schedule can be adapted to that of measles vaccination. Long-term epidemiological surveillance of varicella in Germany is considered to be necessary, so that secular trends in disease prevalence and immune status can be detected in timely fashion and the vaccination program can be changed accordingly, if necessary.

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