Fifteen years of routine childhood varicella vaccination in the United States—strong decrease in the burden of varicella disease and no negative effects on the population level thus far

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Varicella (chickenpox), the primary manifestation of varicella-zoster virus (VZV) infection, is a usually mild disease in young children (1). Nevertheless, significant complications, e.g., bacterial super-infections of cutaneous lesions or neurological manifestations, occur in all age groups, with a higher incidence among older children, adolescents and adults (1-3). Without vaccination, VZV infection in temperate climates affects about 90% of children up to 10 years of age (4). After primary infection, VZV can remain latent in the neuronal ganglia and, after reactivation, may result in herpes zoster (shingles), with the highest burden of disease in the older population (1).

Various live-attenuated varicella vaccines are currently licensed, either as monovalent vaccines or as combined measles-mumps-rubella-varicella vaccines (5). Thus far, varicella vaccines have been shown to be highly effective and safe in clinical and epidemiological studies, with a higher efficacy after two doses (4,6,7).

To date, to our knowledge, nationwide routine childhood varicella vaccination programs have been established in 16 countries, and regional programs in three countries. In many other countries the introduction of routine vaccination is currently being discussed (4,5). The aim of routine varicella vaccination is to decrease the burden of varicella disease, of varicella-associated complications and fatalities, and of varicella-associated costs.

However, the overall impact of routine vaccination on VZV epidemiology (regarding both varicella and herpes zoster) is not fully understood. There is concern that widespread routine varicella vaccination might result in negative effects at the population level, and several countries have decided to postpone a decision on routine varicella vaccination until more information is available (4). One major concern is that routine vaccination may result in more varicella cases in older age groups, with a potentially more severe course of disease (8): first, reduced wild-type VZV circulation due to routine immunization programs might lead to delayed contact with the virus in unvaccinated individuals and, hence, an increase in the number of susceptible older children, adolescents and adults; secondly, vaccine-induced immunity might wane with time, resulting in more cases in adult life. A further major concern is that reduced wild-type VZV circulation might also lead to an increase in the frequency of herpes zoster in the unvaccinated older population. In individuals with previous wild-type varicella infection, exposure to varicella later in life is hypothesized to be necessary for boosting the VZV specific immunity and thereby providing a degree of protection against herpes zoster (9). Mathematical modelling predicts that reduction of this exogenous boosting by routine varicella vaccination might result in higher herpes zoster incidence rates and in an age shift with herpes zoster occurring at an earlier age among adults (4,8).

The United States were the first country to introduce routine varicella vaccination for young children. Before the introduction of routine vaccination, there were an estimated 4 million varicella cases, 10,000 varicella-associated hospitalizations and about 100 fatalities each year (10). In 1996, a single dose was recommended in children 12-18 months of age (6). To counteract potential age shift effects, catch-up vaccinations for susceptible older children up to 12 years of age were also recommended at that time (6).

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Already under the one-dose schedule, varicella incidence, hospitalizations and deaths declined considerably, by 65-90% (10). Following multiple outbreaks observed 5 to 10 years after introduction of the one-dose schedule, a second dose for 4- to 6-year-old was recommended in 2006, resulting in a further decline in varicella incidence (10).

One of the longest and largest investigations currently available on the impact of routine varicella vaccination in the United States was conducted by Baxter *et al.* and recently published in *'Pediatrics'* (11). The authors examined the changes in varicella epidemiology since the introduction of routine vaccination over a period of almost 15 years, in the light of concerns about a potential age shift to older children and adolescents which might occur with increasing coverage and reduced levels of VZV circulation (11).

Baxter et al. conducted their study in the 2 to 3 million member population of 'Kaiser Permanente', a health care delivery system in Northern California. Members obtain almost all their medical care within this system, and the system provides information on an individual's vaccination status as well as on hospitalizations. The authors performed a series of five cross-sectional telephone surveys (in 1995, 2000, 2003, 2006, and 2009), each on a random sample of about ~8,000 children 5 to 19 years of age. Information was collected on varicella vaccination status, occurrence of varicella disease during the past year (incidence) or earlier (varicella history). Varicella disease was reported by parents or self-reported by adolescents; medical confirmation was not required. Additionally, the authors determined varicellaassociated hospitalizations as an indicator for more severe varicella disease. In the entire member population (including adults), they identified patients with varicella reported as primary diagnosis from computerized hospital discharge records.

From 2000 to 2009, the authors reported a rapid increase in first-dose vaccination coverage among 5- to 19-year-old children. In the 2009 survey, 91% of all children 5-19 years of age without a varicella history were reported as being vaccinated, with an extremely high coverage rate (about 99%) reported in the groups 5-9 and 10-14 years of age. Forty percent of all participants in the 2009 survey had also received a second dose of vaccination (recommended since 2006). As expected, second-dose coverage was higher among 5- to 9-year-old (73%), but 24% coverage was observed even among 15- to 19-year-old, largely due to catch-up vaccination programs. The proportion of children and adolescents 5 to 19 years of age, who had not been vaccinated against varicella and were still susceptible, decreased to less than 10% between 1995 and 2009, even among 15- to 19-year-old. This indicates that almost all susceptible children covered by the 1996 routine recommendation were reached, and that catchup vaccination programs for adolescents were also largely successful.

Between 1995 (pre-vaccination baseline) and 2009, incidence rates of varicella in 5- to 19-year-old declined by 90-95%, overall and in all age categories. It is interesting that, after an initial decrease between 1995 and the 2003 survey, incidence rates in children 5 to 9 and 10 to 14 years of age were 35% to 60% higher than in 2003 in the 2006 survey. It should be kept in mind that the observed increase was based on a very small number of varicella cases and, hence, chance may have played a role. Nevertheless, it is also possible that the increase was due to the initially missing second dose of vaccine necessary for long-term protection. This hypothesis is supported by the renewed decrease observed after the introduction of the two-dose schedule in 2006, with the 2009 survey showing the lowest incidences in all age groups.

For all ages including adults, a large (90%) decline in varicella hospitalization rates was observed between 1995 and 2009. For hospitalized patients below 30 years of age, the strongest decline was found among children 0 to 4 and 5 to 9 years of age, with no more hospitalizations reported in 2009, compared to hospitalization rates of 12.4 and 4.7 per 100,000 person-years, respectively, before the routine vaccination program. Hospitalization rates in the other groups below 30 years of age also declined compared to the pre-vaccination baseline, with the least pronounced decrease found among the 15- to 19-year-old. Overall, lower hospitalization rates than at baseline were observed in all age groups and survey years, an indication of herd protection effects of routine varicella vaccination even in the mainly unvaccinated older age groups.

A potential limitation of the study was the possible misclassification in participant-reported varicella without medical confirmation. On the one hand, other types of rashes might have been reported as varicella. On the other hand, mild varicella disease, as is typical for breakthrough in varicella-vaccinated children, may have been missed and, hence, the effectiveness of the vaccine might have been overestimated to some degree. A further limitation was a likely underestimation of varicella hospitalization rates, as these were calculated solely from data on patients with varicella as primary diagnosis.

The study showed the strong impact of childhood one-

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dose routine varicella vaccination in all age groups, and suggested an additional effect from two-dose vaccination on the burden of disease. There was no indication of a shift to older age groups during the observation period of 15 years. Thus, the present study shows an impressive impact on varicella disease burden, both directly and by indirect protection of unvaccinated susceptible individuals who benefit from high immunization levels in the population.

The observed pattern of decline was in accordance with trends found in previous varicella surveillance studies from the Unites States, with shorter observation periods after recommendation (10). Additional effects of the two-dose schedule and strong herd protection effects were recently reported also in other surveillance areas in the United States (10,12). However, it should be kept in mind that all data by Baxter et al. were collected in a health care setting providing excellent conditions to promote varicella vaccination. The study population was highly compliant, as demonstrated by the very high level of coverage (11). In general, high and sustained varicella vaccination coverage is reached in large parts of the United States, where a two-dose varicella vaccination schedule and catch-up vaccination programs are widely implemented, and where compliance can be enforced by school entry regulations (13). It was convincingly demonstrated by Baxter et al. that high coverage conditions can effectively prevent the age shift to older children and adolescents due to a strong increase in herd protection. Mathematical models predict an age shift for coverage rates below 80-85% (4,8). In the Baxter et al. study, almost all children 5 to 14 years of age without a history of varicella had been vaccinated, and more than 50% had already received two doses. The proportion of children 15-19 years of age who were still susceptible was low, and it can be assumed that due to the high coverage in younger children only a small probability remained for being exposed to wildtype varicella.

What has happened thus far outside the United States, in countries where routine varicella vaccination was introduced more recently or where the conditions to reach high and sustained coverage might be less favorable? In both non-European [see table from (14), (15)] and European countries and regions (4,16), even with lower vaccine coverage rates (between 60% and 90%) an impressive decline in the burden of varicella disease has been reported under one-dose and especially under two-dose varicella vaccination schedules.

In Europe, Germany was the first country to introduce nationwide routine varicella vaccination, with a one-dose schedule at 11-14 months of age recommended in 2004

and a recommendation for a second dose during the second year of life in place since 2009. For the birth cohort 2009, nation-wide first-dose coverage among 2-year-old was estimated as 87%, and second-dose coverage as 64% (17). During the period 2005 to 2012, a nation-wide reduction in varicella cases and complications by 84%, and 81%, respectively, was reported, and no indication for an age shift has been observed thus far (4). Considerable reduction in the burden of disease, absence of indications of an age shift, and herd protection effects were also reported for a German region where coverage had increased more slowly and was still below 70% during the time of observation (14). Even in this area, varicella incidence both in outpatients and hospitalized patients had declined already by ~70% and ~40%, respectively, during the relatively short sixvear observation period (14). Overall, there is mounting evidence of the effectiveness of varicella vaccination, thus far without any indication of the age shift in varicella incidence predicted by mathematical models, which might underestimate herd protection effects.

Nevertheless, continued and long-term surveillance is advisable in all countries where routine varicella immunization has been established, as a number of important questions remain to be answered. The duration of immunity after two doses is still unknown (5). In the case of waning immunity over longer time and continuing wildtype VZV circulation, an increase in breakthrough varicella in older individuals might therefore still occur. Thus far, only rare cases of breakthrough varicella after two doses have been observed, and these are usually reported as being milder cases (7,18), but frequency and severity may increase over time, as has been shown for breakthrough after one dose (19). Furthermore, in view of the ability of VZV to establish latency and be reactivated many years later, more information on the epidemiology of both wild-type and vaccine-type herpes zoster in the long term will be helpful. Interestingly, recent data on varicella-vaccinated children has been encouraging, indicating a lower incidence at least of pediatric herpes zoster after varicella vaccination (20). Future VZV surveillance should also include the molecular level, as recombinant VZV may occur in individuals carrying both latent wild-type and vaccine-type VZV (21). Individual cases of such wild-type/vaccine-type recombinant VZV have recently been found in children with herpes zoster (20,21), although no indication of an increase in severity of the disease has been observed yet. Development of future varicella vaccines without the potential to establish latency (for example, inactivated or subunit vaccines) would

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avoid vaccine-type herpes zoster (22), and could help further reduce reservations against routine varicella vaccination.

In conclusion, the data of Baxter *et al.* and other studies from the United States, as well as current data from other countries, have provided convincing evidence of the high effectiveness of routine varicella vaccination. They demonstrate the strong impact of a one-dose and especially a two-dose vaccination schedule on varicella, a disease whose burden has often been underestimated.

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