

# Changes to the varicella and pertussis immunisation schedule in Germany 2009: Background, rationale and implementation

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## Citation style for this article:

Citation style for this article: Wiese-Posselt M, Hellenbrand W. Changes to the varicella and pertussis immunisation schedule in Germany 2009: Background, rationale and implementation. *Euro Surveill.* 2010;15(16):pii=19548. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19548>

This article has been published on 22 April 2010

In July 2009, the German Standing Committee on Vaccination (STIKO) modified its recommendations for varicella and pertussis vaccination, based on newly available data on disease epidemiology, vaccine effectiveness (VE) and safety, and an evaluation of the feasibility of the recommended immunisation strategy. The recommendation for varicella vaccine now includes a routine two-dose schedule with the administration of the first dose at the age of 11 to 14 months and the second dose at the age of 15 to 23 months, with a minimum interval of four weeks between these doses. Furthermore, STIKO recommended adding a one-time pertussis booster to the adult vaccination schedule to expand the cocoon strategy in place since 2004. The recommendation of a booster vaccination with an acellular pertussis vaccine every 10 years for persons employed in the care of pre-school children and for healthcare personnel in paediatric, gynaecologic and obstetric health facilities was extended to persons employed in schools and in other institutions caring for older children, and to all healthcare personnel. These recommendations were based on available epidemiological data showing an increase in incidence from 7-10 cases per 100,000 inhabitants in 2002-2004 to over 30 by 2007. Moreover, the high burden of pertussis in infants at 94 hospitalised cases per 100,000 infants in 2007 suggested that the previous cocoon strategy was insufficient.

## Introduction

The German Standing Committee on Vaccination (STIKO) is a board of honorary experts in the fields of vaccinology, infectious disease epidemiology, microbiology and virology, paediatrics, evidence-based medicine and others. STIKO members are appointed by the Federal Ministry of Health every three years. STIKO reviews its recommendations for vaccination on an annual basis. Its decision-making process is based on published data on disease epidemiology, vaccine effectiveness (VE), and safety, and on the feasibility of the recommended immunisation strategy. STIKO is not responsible for a health economic assessment of

the effect of vaccination. In this paper we communicate the major modifications to the immunisation schedule in Germany implemented in July 2009 and we detail the scientific rationale for the changes [1]. The main changes were the addition of a second dose of varicella vaccine to the routine childhood vaccination schedule and the recommendation of a single pertussis booster for adults.

So far, Germany is the only country in Europe to have introduced a nationwide recommendation for routine childhood varicella vaccination. Since the introduction of, initially, a one-dose varicella vaccination in children, a significant reduction of varicella cases in children was observed in a nationwide sentinel surveillance system, as recently published by Siedler *et al.* [2]. This positive experience with varicella vaccination in Germany and the deliberations of the STIKO on the introduction of a two-dose varicella vaccination schedule might be helpful for other countries in Europe in their decision making process.

## Second dose of varicella vaccine in children

In 2004, STIKO recommended routine varicella vaccination for all children older than 11 months with the aim of reducing varicella associated morbidity and the reduction of the burden of disease [3]. A single dose of monovalent varicella vaccine was recommended at 11 to 14 months of age and at that time, two licensed vaccines were available for this purpose in Germany, Varilrix and Varivax. In 2006, the measles-mumps-rubella-varicella (MMRV) vaccine (Priorix-Tetra) was licensed for administration in two doses at least four weeks apart [4]. In 2008, the licensed immunisation schedule of both monovalent varicella vaccines changed to a two-dose scheme for all children [5,6].

Based on epidemiological data from Germany and the United States (US) as well as newly available data on varicella zoster virus (VZV) vaccine immunogenicity and effectiveness after one and two doses of VZV-containing vaccines, STIKO decided to follow

the change of vaccine licensures and recommended a routine two-dose vaccination strategy in children. The aim of this recommendation is to reduce the number of varicella outbreaks, the number of cases with varicella breakthrough illness (BI) and the transmission of VZV to susceptible persons with a higher risk for severe varicella disease such as pregnant women and immunocompromised patients.

### **Epidemiological data from Germany and the US**

Varicella is not notifiable in Germany. Therefore, a country-wide sentinel project on varicella and zoster epidemiology was established in Germany in April 2005 [7,8]. The constitution of the sentinel system and its first results covering the time frame April 2005 to March 2009 have been published recently [2]. Since sentinel surveillance cannot provide population-based data, varicella incidence and vaccination coverage cannot be calculated directly. However, from 2005 to 2009, physicians reporting to the sentinel diagnosed successively fewer children with varicella with a significantly decreasing trend over time, while they administered a rapidly increasing number of varicella vaccines for first doses and since 2008, second doses of VZV-containing vaccine as well. A stable number of sentinel physicians reported around 60% fewer varicella cases in the 2008-9 season than in the 2005-6 season. Concurrently, a rising number of varicella BI was reported over the observation period [2,8].

Available information on vaccine coverage for the federal state of Schleswig-Holstein shows that coverage in children under 24 months of age with one dose of VZV containing vaccine, increased from 11% in 2006 to 83% in 2008 [personal communication Hans-Martin Bader and Maik Ludwig].

In 2008 and 2009, the RKI investigated seven varicella outbreaks in day-care centres including 631 children with available varicella vaccination information [9]. The attack rate was 13% in vaccinated children and 48% in unvaccinated children, resulting in an overall VE of 71% [95% confidence interval (CI): 57-81] in the multivariable analysis [9]. VE differed significantly by disease severity and number of doses administered. VE of one dose and two doses of VZV-containing vaccines was estimated to be 62% [95% CI: 43-75] and 94% [95% CI: 75-98], respectively. Furthermore, results of outbreak investigations in Germany suggest that VE and the risk of varicella BI are not uniform for the different varicella vaccine products available in Germany [9].

The US varicella vaccination programme implemented in 1996 recommended one dose of monovalent varicella vaccine at the age of 12 to 18 months and achieved over 90% reduction in varicella morbidity in children between 1995 and 2005 [10,11]. Since varicella outbreaks continued to occur and an increasing number of cases with varicella BI was observed in active surveillance areas, the US Advisory Committee

on Immunization Practices (ACIP) recommended a second dose of varicella vaccine for all children aged four to six years in 2007 [12]. However, when applying these data to the German situation, it must be kept in mind that there is only one vaccine (Varivax) available in the US and a high vaccination coverage over 90% in children under three years old has been achieved for a prolonged period of time [11].

### **Effectiveness, immunogenicity, and safety of VZV-containing vaccines**

VE after one dose Varivax was estimated at 84.5% (range: 44-100) in a recent review [13]. Estimates from three epidemiological studies on the VE of one dose of Varilrix range from 20 to 92% [14-16]. So far no data on VE after two doses of Priorix-Tetra have been published.

In 2008, the licensed immunisation schedule of both monovalent varicella vaccines changed to a two-dose scheme for all children [5,6]. The regulatory authorities based this change of licensure on immunogenicity data after one and two doses of VZV containing vaccines and on a large epidemiological study by Kuter *et al.* conducted in the US in the 1990s using Varivax, although at a higher potency than available licensed vaccines [17-19]. In this study the risk of developing varicella 42 days after vaccination was 3.3-fold lower in children who received two doses of Varivax compared with those who received only one dose ( $p < 0.001$ ). The estimated vaccine efficacy for the 10-year observation period for one or two doses Varivax was 94.4% and 98.3%, respectively ( $p < 0.001$ ). This efficacy estimate was based on comparison with historical data of annual varicella incidences in unvaccinated susceptible children. In a randomised controlled trial in 10-21 month-old VZV seronegative children an over 20-fold higher geometric mean titre (GMT) of VZV antibodies was observed in children with two doses of Priorix-Tetra compared with children vaccinated with only one dose of a monovalent varicella vaccine [17]. However, the study by Kuter *et al.* showed that GMTs decreased to similar levels within several years regardless of the number of doses (one or two) applied [19]. Therefore, the reliability of VZV antibody levels as a correlate of protection after vaccination remains unclear.

A good safety profile of VZV-containing vaccines available in Germany has been reported [4-6]. However, for the MMRV vaccine ProQuad, which is only available in the US, febrile seizures were observed more frequently post-vaccination than after simultaneous administration of MMR and monovalent varicella vaccines in children under two years of age. [20].

### **Feasibility of routine two-dose varicella vaccination in children**

The first dose of VZV-containing vaccine is recommended at the age of 11 to 14 months and the second dose at the age of 15 to 24 months. Thus, varicella vaccination can be administered simultaneously with the

measles-mumps-rubella (MMR) vaccination using a monovalent varicella vaccine plus an MMR vaccine or using the licensed MMRV vaccine. However, varicella vaccination can be offered to any child aged 11 months or older. A second dose is also recommended for all children who thus far received only one dose of VZV-containing vaccine.

### **Pertussis vaccination of adults**

In July 2009, STIKO recommended adding a single pertussis booster to the adult vaccination schedule against pertussis, in order to expand the cocoon strategy which recommended pertussis vaccination for all adults with close contact to infants since 2004. The 2004 recommendations also included a booster vaccination with an acellular pertussis (ap) vaccine every 10 years for persons employed in the care of pre-school children and for healthcare personnel in paediatric, gynaecologic and obstetric health facilities. These were expanded to include persons employed in schools and in other institutions caring for older children, as well as all healthcare personnel. The new recommendations were based on careful analysis of available epidemiological data on the disease burden in adults as well as data on immunogenicity, effectiveness and safety of available vaccines. The aim of the updated recommendations is to decrease pertussis-related morbidity in adults as well as in non-immune, unprotected contacts, particularly infants [21;22].

### **Epidemiological data from Germany for adults**

Pertussis is a notifiable disease in five of the 16 German federal states. Despite increasing vaccination coverage among children at school entry to over 93%, the incidence of pertussis in adults in the states with statutory surveillance increased from 7-10 cases per 100,000 inhabitants in 2002-2004 to a maximum of 32 in 2007, decreasing only slightly to 30 in 2008 [22;23]. The average age of notified cases increased from 15 years in 1995 to 42 years in 2008, with a concomitant increase in the proportion of cases older than 19 years (adult cases) from 20 to 75%. Sentinel surveillance performed from 2000-2004 [24] estimated a similar annual incidence in an east and a west German city, 169 and 160 pertussis cases per 100,000 adult inhabitants, respectively, translating to a nationwide estimated incidence of 160. However, pertussis incidence increased according to statutory surveillance in the years following conclusion of this sentinel study. These figures thus suggested a marked under-ascertainment in the statutory surveillance system. In addition, the burden of pertussis in infants remains high with an incidence of 94 hospitalised cases per 100,000 infants in 2007, implying that the cocoon strategy implemented in 2004 was insufficient.

The majority of pertussis outbreaks notified from 2002-2007 in the five German federal states with statutory pertussis surveillance involved children older than nine years (70% of cases in outbreaks with more than five cases), which was the rationale for expanding the

recommendation for pertussis vaccination to persons employed in schools and other institutions involved in the care of older children. A Canadian study calculated that healthcare personnel had a 1.7-fold elevated risk for pertussis compared with the general population [25]. Numerous pertussis outbreaks among healthcare personnel involved in the care of adults have been published [26] and a modelling study in the United Kingdom estimated a high incidence of pertussis in hospitalised elderly patients [27].

Adults with pertussis often fail to present with the full-blown clinical picture, but nonetheless suffer significant morbidity. In the above mentioned surveillance study by Riffelmann *et al.* [24], the median duration of the primary symptom, cough, was 48 days (maximum: 72 weeks) and on average, patients consulted their general physician 5.4 times and 27% were referred to a specialist. Antibiotics were prescribed for 53% of patients and 13% received steroids. In various case series between 23% and 28% of all adult patients with pertussis suffered complications, including sinusitis, otitis media, incontinence, weight loss, rib fractures, syncope and pneumonia [24;25;28;29]. Hospitalisation was reported in 1 to 3% of adult pertussis cases [25;29-31].

### **Effectiveness, immunogenicity and safety of pertussis vaccines**

Effectiveness of vaccination with an ap vaccine containing three pertussis antigens was demonstrated in adults in one randomised controlled trial, which was, however, based on the observation of only 10 pertussis cases in total: one case amongst 1,391 tetanus-diphtheria-acellular pertussis (Tdap)-vaccinated participants, and nine pertussis cases amongst 1,390 hepatitis A vaccinated participants [34]. Vaccine efficacy was estimated at 92% (95% CI 32-99). Numerous studies have demonstrated immunogenicity of pertussis vaccines in adults equivalent to that observed in studies in children in which clinical efficacy was shown [32]. These studies have also demonstrated that the safety and reactogenicity of ap vaccines is similar to that of Td (tetanus-diphtheria) vaccines.

### **Cost-effectiveness**

Lee *et al.* [33] performed a cost-effectiveness analysis for vaccination of adults in Germany using conservative estimates of pertussis incidence and including direct costs as well as indirect costs due to loss of work by means of a Markov model. This suggested that one time vaccination of around 62% of adults would be cost-effective and possibly cost-saving, at a cost of 160 Euros per pertussis case prevented. Two other models tailored to the US situation came to similar conclusions [21;34;35].

### **Feasibility of implementing a one-time adult pertussis booster**

Implementation of an adult booster is considered feasible. Telephone surveys in Germany revealed a high



acceptance of tetanus vaccination, with 75% of a population based sample of adults reporting having received a tetanus-containing vaccination in the past 10 years (unpublished data, RKI). However, it is essential that Tdap vaccines are made widely available for tetanus post-exposure immunisation in emergency settings. In addition, efforts are needed to improve vaccination coverage in adolescents, which remains low at 36% [36].

## Conclusions

### Varicella vaccination

Germany is currently the only country in Europe that includes varicella vaccination in the routine immunisation schedule for children. Results from sentinel surveillance show that the recommendation of routine varicella vaccination for all children older than 11 months in 2004 has had a positive effect on the overall burden of varicella in Germany [2]. Based on immunogenicity data after one and two doses VZV-containing vaccines (indirect evidence) and based on the findings of the study of Kuter *et al.*, licensures of both monovalent varicella vaccines changed to a two-dose schedule [17-19]. With respect to recent epidemiological findings in Germany and from the US, where varicella vaccines are included in the routine immunisation programmes since 1996 [2,11], STIKO decided to follow the change of licensure and recommended a second dose for all children in July 2009. As published VE estimates vary widely, and one VZV vaccine (ProQuad) has been associated with an increased risk of febrile seizures in children less than 2 years of age [13-16,20], there is a need for additional post-marketing data on safety and effectiveness of VZV-containing vaccines. A population-based VZV surveillance system should be established in Germany to evaluate the effect of routine varicella vaccination in children and to monitor varicella and herpes zoster incidences in all age groups.

### Pertussis vaccination

As herd protection has been demonstrated after implementation of pertussis vaccination in children [37;38], it seems reasonable to assume that vaccination of adults can lead to reduction of disease in unprotected individuals, particularly infants. Furthermore, a modelling study has estimated that around 34% of all transmission of pertussis to infants occurs via less close contacts [39]. Both natural and vaccine-induced immunity is not lifelong [40], waning immunity in the face of decreased natural boosting in conjunction with increasing vaccination coverage in children [41] – is likely the most important factor leading to high disease burden in adults. The aim of the addition of a pertussis booster to the adult vaccination schedule is thus to reduce the overall pertussis disease burden. The implementation of the changes to the adult pertussis vaccination schedule will be evaluated in regular population-based telephone interviews soliciting data on vaccination status, and through analysis of routine surveillance data available from the former East German states, hospital discharge statistics and the established laboratory

surveillance of molecular genetic characteristics of *B. Pertussis*.

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