Routine childhood varicella vaccination in Germany – well-founded?

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Abstract

Background: Varicella is the most frequent vaccine preventable disease of childhood inGermany. Though usually mildly proceeding severe complications may occur, particularlyamong pregnant women, neonates, adults and the immunocompromised. Later in life 10-20% are afflicted by herpes zoster (HZ) through reactivation of the dormant varicella zostervirus (VZV). With regard to >750 000 varicella cases annually and consequent societal costs Germany has introduced VZV immunization into the routine childhood vaccination schedule in July 2004. As this recommendation is a matter of controversial discussion wereconsidered the underlying data in order to revise it. **Method**: A literature search about VZV in developed countries was performed regarding publications from 2001-2005 on disease burden, vaccination including cost-effectiveness and public perception. Available data were.summarized and analyzed with regard to the current VZV vaccination recommendation in Germany. **Results**: Data on basic aspects of VZV vaccination vary considerably:Complications of varicella infections occur in >1% children up to ≤6% of all cases,hospitalization rates range at 0,85-24,7/100 000 person years, mortality at 0,01-0,1/100 000 person years. The available vaccine, a life attenuated monovalent preparation, has been empirically proven to be safe and efficacious with 80-100% of seroconversion. Yet risks of lacking persistance, of a rise in the average age of infection followed by a higher rate of complications and of a growing incidence of HZ could not be excluded. Statements on the effective dosage go from 439 to15 850 PFU1. Effectiveness in terms of decreasing morbidity requires a minimum of 70% coverage, elimination acc. to author 85-97%. Breakthrough infections (milder than natural) occur in at least 1-5% of vaccinees, risk factors include low dosage, 3-5-year interval since immunization and vaccination age <15 months.Costeffectiveness of general VZV vaccination strategies of healthy populations has been.examined by simulation studies only, with contradictory results: Net cost savings were deduced either concerning both health care and societal costs, or solely in case of assuming high treatment costs, or only from averted unproductive days for parents. Targeted vaccination of immunocompromised, healthcare workers and seronegative pre-adolescents however appeared cost-effective in any investigation. Public support and acceptance of VZV vaccination in Germany has to be questioned as generally merely 59% of recommended immunizations are performed, as the top organizations of sickness funds rejected to cover costs and as physicians appear to be "tired" of motivating people to get vaccinated. **Discussion**: The German VZV vaccination recommen-dation refers predominantly to empirical data from 10 years vaccination programme in the U.S. and to publications claiming a comparatively high disease burden, an advantageous cost-benefit ratio and an achievable coverage of 85% for Germany. Considering the uncertainty of these assumptions a targeted vaccination schedule and its careful realization should be preferred.

1 Plaque forming unit

Introduction

Varicella vaccination has been standard for all children and young people in the United States (USA) since 1995, with good results (23,26). Germany is the first country in the EuropeanUnion (EU) to introduce universal varicella childhood vaccination.(20) With regard to anestimated over 750 000 varicella cases annually and consequent societal costs the StandingCommittee on Vaccination at the Robert Koch Institute (STIKO) in Germany, recommendeda Universal childhood immunisation against varicella in July 2004(42). In doing so, they expanded their previous recommendations to vaccinate particular risk groups (and their contacts), and for young people who had not had varicella . Recommendations that were ften not followed in the past(20).

Currently vaccination is recommended at the age of 11 - 14 months, preferably together with MMR vaccine or 2 weeks later (42).This decision of STIKO has become an issue of debate especially since a year earlier they had recommended against such a programme.

The success of a universal vaccination recommendation depends on several factors including disease burden, availability of a safe and effective vaccine, cost effectiveness of the vaccination and public perception. Such a programme should rashly achieve high and sustained levels of coverage. Concerning varicella vaccine there are also certain issues of controversy which should be considered. Potential harm that may occur as a result of vaccination include immediate adverse reactions, transmission of varicella from vaccinees, an increased risk of zoster, and a shift in varicella cases to an older age group (and hence more severe disease), waning immunity with time after vaccination especially with a lack of the boosting effect of wild-type virus circulation.(47).

The objective of this paper is to review the universal varicella vaccination recommendation in Germany and the underlying data in this regard.

Methods

Pubmed, Medline, Cochrane Library, Embase, Google were searched in the period between October 2005 to Mid February 2006. Publications from the Eouropean Union and the United States in the period between 2000-2006 were included if they addressed vaccine effectiveness and safety, disease burden, cost-effectiveness, public perception. The reference lists of the studies were hand searched. Language was restricted to English and German.

To find data specifically related to Germany; Medline, Springer, Thieme, Deutsches Ärzte Blatt , Robert Koch Institute, World Health Organisation, German Federal Statistical Office Eurosurveillance and Krankenkassenvereinigung websites were searched.

Published studies were finally included if they: [1] considered healthy, human subjects vaccinated with VZV vaccine; [2] were clinical or epidemiological studies addressing the vaccine or the incidence of varicella and zoster; [3] reported results from the universal vaccination programme in the United States; [4] provided information on the cost-effectiveness or cost-utility of varicella vaccination programmes both considering the possible impact on herpes zoster and without this consideration; [5] reported relevant data in Germany.

Outcome measures considered were: efficacy, effectiveness, safety; VZV and HZ epidemiology in Germany, the US (pre- and post- vaccination era) and the EU; vaccination rates in Germany; waning or boosting of immunity; impact of vaccination on HZ; cost-effectiveness.

Data were extracted with regard to Critical Appraisal Tools developed by the Critical Appraisal Skills Programme (CASP) (40). A descriptive analysis was carried out aiming at covering the broad range of statements concerning issues crucial to mass vaccination against varicella.

Results

Vaccine effectiveness and safety

Early studies indicated that healthy children gained about 85% protection against household exposure after a single dose of vaccine, with breakthrough disease occurring in about 15% (57). There have been different trials on the effective doses of the vaccine. One RCT showed no difference in vaccine effectiveness between doses varying from 439 to 3625 PFU (45), while another showed decreased effectiveness below 1260 PFU(53).The study showing no difference had a longer duration of follow up (mean 4.3 years compared to 29 and 35 months), but relied on self reporting of disease (45). Lim et al. showed that doses less of 501-631 PFU resulted in breakthrough disease more commonly than doses of 7943-10 000 PFU (34). In a placebo controlled trial dose of 17000 PFU was reported to be 95% efficacious over 7 years (150).

In a 10-year follow-up study of children who received the varicella vaccine it was determined that an initial injection followed by a booster injection was more effective (98.3%) than a single injection (94.4%) (32).

A post- vaccination case control study by Vasquez et al. (54) demonstrated that the vaccine's effectiveness in the first year is reduced if administered at <15 months (73% before 15 months compared to 99% after 15 months); others have shown that adult vaccinees have a lower degree of protection (70%) than children (21), and 3-4 times the breakthrough rate in vaccinated, healthy children (1).

Outbreak studies in USA show an effectiveness between 44 - 88% (10-12).A recent report of a varicella outbreak at a day-care centre in the U.S. demonstrated a low vaccine efficacy rate of 44%., however the result had a long confidence intervals.(18) The results of some outbreak investigations are outlined in (Table 1).

Current evidence indicates that varicella infections in previously vaccinated individuals are due to wild-type virus rather than the vaccine strain (47) . The vast majority of breakthrough cases are milder than natural cases (60,47). There is evidence that breakthrough infections in vaccinated, healthy persons with 50 lesions or more can be as infectious as varicella in unvaccinated persons(77, 50).

The most cited risk factors for breakthrough varicella include the following: (1) 3-5-year interval since immunization and (2) immunization at the youngest ages, especially 12 months (26). Other factors that contribute to breakthrough include age at immunization, viral titer of the vaccine dose, course of immunization (i.e. with or without booster injection) and immunocompromised status(54). Explanations for breakthrough varicella include a lessened immune response among the youngest recipients of the vaccine. Another possibility is genetic variation among circulating VZV strains.(26)

Since vaccination can induce mild skin lesions containing live virus, there has been concerns about transmission of the vaccine strain. Cases of transmission have been reported rarely from adults and children with varicella like rash following vaccination (46). Brunell and Argaw recently reported transmission of vaccine strain virus from a vaccinated child with zoster to their vaccinated sibling, resulting in mild chickenpox (9). A post-licensure report using passive surveillance methods has also found very few cases of possible vaccine strain transmission(60).

No serious adverse reactions have been reported in controlled trials (56,31). Post licensure evidence is conflicting, with one review of 89 000 vaccinees belonging to a health maintenance organisation finding no serious reactions, while Wise et al. found a temporally related serious adverse event rate of 2.9/100 000 doses (47,60). According to Wise et al.(60)Over the first three years after implementation of universal vaccination programme US Vaccine Adverse Event Reporting System (VAERS) received 6574 case reports of adverse

events in recipients of varicella vaccine, a rate of 67.5 reports per 100,000 doses sold. Approximately 4% of reports described serious adverse events, including 14 deaths (60). From post marketing surveillance, we know that at least 1 child died of chickenpox 21 months after vaccination (59). Wirrell et al have reported 2 cases of stroke 5 days and 3 weeks following varicella vaccination (58).

Table 1. Out break investigation studies and the respective effectiveness of varicella vaccine

Study (year) (ref)	**Study Design**	Number of vaccinees	Number of unvaccinated	Number of doses	Duration of follow up	**Effectiveness (range)** against**	
						All forms of varicella	Moderate-severe varicella
Buchholz et al. (1999) (10)	**Cohort outbreak investigations**	40	19	1		**76%**	
Dworkin et al. (2002) (15)		146	63	1		**88%**	
Galil et al. (2002)		25	18	1		**44% (7-66)**	**86% (39-97)**
Galil et al. (2002) (18)		80	20	1		**79% (66-88)**	**95% (84-98)**
Tugwell et al. (2004) (19)		152	7	1		**72 % (3-87)**	
Haddad et al. (2005) (28)		26	57	1		**87%**	
CDC[j] (2004) (12)		442	15	1		**84.7% (77.4-89.7)**	**97.6% (95-98.9)**

** 95% confidence interval

[i] overall vaccination coverage was 37%.

[j] Centers for Disease Control and Prevention (CDC)

Disease burden in Germany

In Germany varicella is not a notifiable disease. It has recently become notifiable in Saxony Anhalt since September 2005.(37) There is an estimated 750,000 varicella cases per year(1). Chickenpox typically occurs in children and a predominance of the cases in the first decade is observed. The sex ratio is equal. In Zoster cases, there is a marked influence of age and sex, on the localization of the involved nerve segments. Zoster is seen in patients of all ages but there is a clear predominance in older patients. The peak of the disease occurrs in the eighth decade. (48)

Studies to estimate the epidemiology and disease burden in Germany include seroprevalence studies, epidemiological surveys, estimation by mathematical modelling, and sentinel surveillance. In addition, ICD data from the Federal State Health Monitoring System are also available.

Epidemiological studies

In a small prospective study in the city of Ansbach all cases were registered for one year and the population-based incidence of chickenpox reported was 42.4 per 10,000 inhabitants and of zoster infections 22.6 per 10,000 inhabitants per year (38).

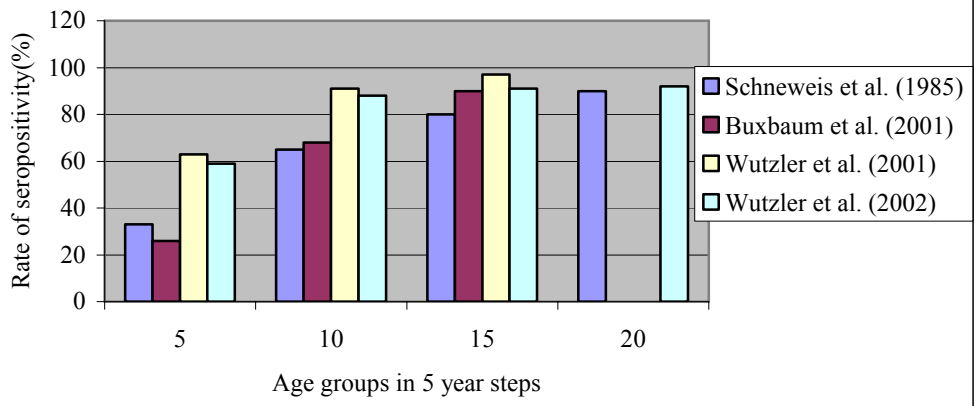
In a later epidemiological survey, data on 1,334 unvaccinated varicella cases were obtained via telephone interviews from physicians and were studied cross sectionally and retrospectively for the year 1999. The German prescription index was used for the representative weighting of both under 12 year old children and over. The incidence of varicella was 760,000 cases for the year 1999 (derived from the German prescriptions index). Regarding a population size of 82 million an incidence rate of 9.27 new varicella cases per 1,000 inhabitants within a year was calculated. 82.4% of the varicella patients were younger than 8 and 10% of diagnosed cases were older than 12 years. The population-weighted varicella complication rate was estimated 5.7%. In the younger population the frequency of complications amounted to 5.9%. (55, 62)

Seroprevalence studies

The seroepidemiological survey by Wutzler et al (63) was cross-sectional and age-stratified. Two serum banks collected between 1995 and 1999 by the Robert Koch-Institute (Berlin, Germany) were available. In their seroprevalence study of 4,602 serum samples from all age groups, Wutzler et al report that by the age of 4-5 years 62.5% (95% CI; 56.0-68.5) of the pre-school children have already been infected with VZV and at the age of 10-11 years 94.2% (95% CI; 91.0-96.0) of children are positive for anti-VZV antibodies.(63) Among the age-group of >40 years old, only few individuals are susceptible for VZV.(63) Buxbaum et al. (11) studied 2,291 serum samples and reported the highest rate of seronegatives in younger children. VZV-seronegativity rates decreased from 74 % to 32 % in younger children. By the age of 15 almost 90% were reported seropositive.(11) Schneweis et al reported 67% seronegativity in children under 5 years of age decreasing to about 35% by the age of 10. By the age of 15, 80% were reported seropositive and 90% were seropositive by 20. (48)

Data on seroprevalence of varicella in Germany is outlined in diagram 1. The results of three other countries can be seen in table 2.

Diagramm 1. Seroprevalence of varicella disease in the first two decades of life in German population indicated by different studies



It can be seen that in earlier studies much lower rates of natural infection are reported in the first decade of life which could indicate an age shift in the older age, however, this can not be observed in the later studies by Wutzler et al. There are also slight differences between the results from the studies reported by Wutzler et al. It can be argued that the sample size of the study by Schneweis is relatively small in comparison to the other studies. Still, the results are similar to those of Buxbaum et al. The acceptable conclusion we can draw is that by the age of 15 years, seroprevalence reaches 90% in the German population.

Table 2. Age- related percentage of prevalence of varicella disease in other countries

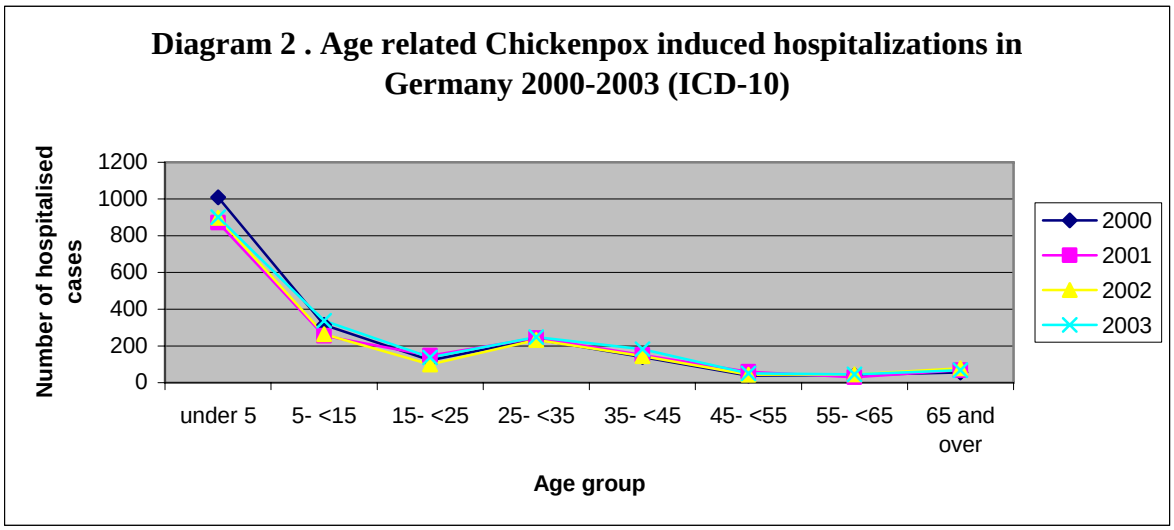
Age	**Coudeville et al. (51)** (1999, France)	**Fairley et Miller(39)** (1996, England & Wales)	**Seward et al.(50)** (2002, USA)	**Bramely et al [a] (49)** (2000, Scotland)
Under 5	**52.6%**	**41%**	**43%**	**82%**
Under 10	**85.8%**		**84.8%**	
Under 15	**91.5%**	**76%**	**92.8%**	**95%**
Under 20	**93.7%**		**95.1%**	

[a] Statutory notification of chickenpox by clinical diagnosis. Laboratory reports for varicella zoster virus in 1998.

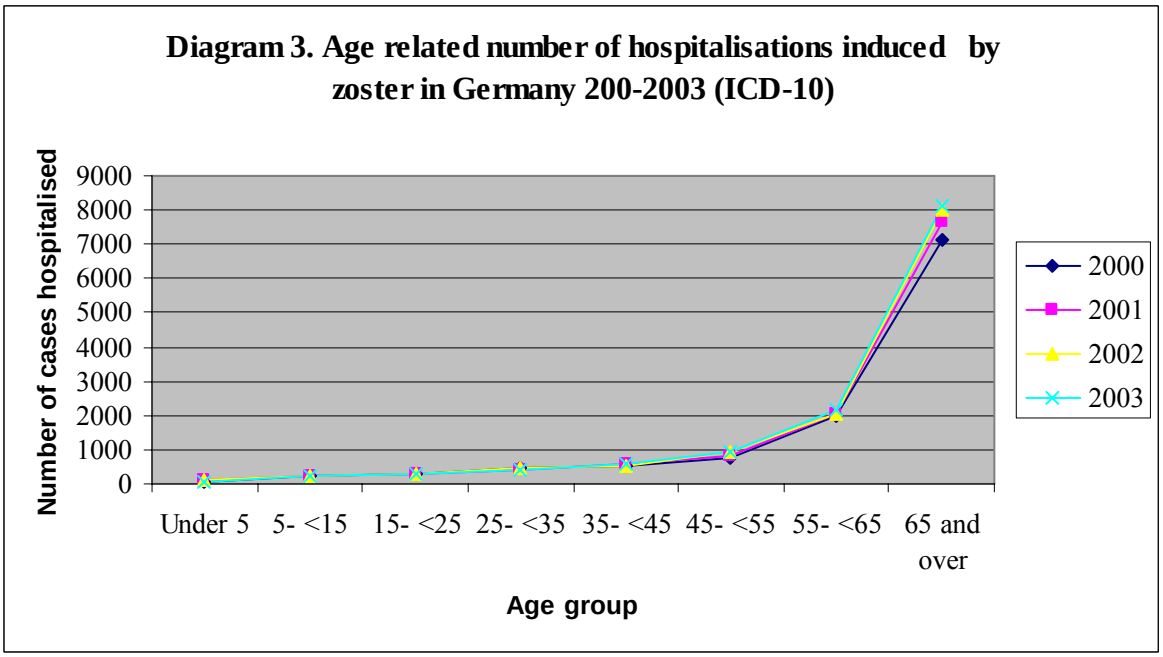
Complications and hospital admissions

The incidence estimates of hospitalizations from the Federal Statistical Office (ICD-data), German Paediatric Surveillance Unit (ESPED), and some studies could be identified:

The Federal Statistical Office and the Robert Koch Institute conduct Federal Health Monitoring as a common task. Data are collected systematically from all German clinics.(16) Based on the ICD- data from 2000-2003 there were on average a total of 1890 hospitalisations, 11,342 total hospital bed stays, 6 days average of length of stay and 7 deaths induced by varicella in all age groups. Zoster caused a mean of 12,261 hospitalisations, 130, 654 bed stay days, 10.65 average length of stay, 81 deaths caused by herpes zoster. The mean and mode of bed stay days for cases under 15 years of age were 5.05 and 5 respectively. The relation between hospital admissions caused by varicella in 2000-2003 is shown in diagram 2.



Although misclassifications can happen in ICD data, trends in the incidence can be observed. The highest rate of admission induced by varicella can be seen in the first 5 years of life at around 1000 cases. Of interest is simultaneous observation of disease trends. A comparison between both diagrams shows that the highest incidence of varicella in children (2000) coincides with the lowest incidence of zoster in the elderly(2000).



In addition to the ICD data there are also estimated incidence rates available from two studies by the "Erhebungseinheit für Seltene Pädiatrische Erkrankungen in Deutschland" (ESPED) which is a German adaptation of the British Pediatric Association Surveillance Unit. (65)

Reporting a 93% response rate in their first study in 1997 a crude incidence of severe chickenpox complications of 0.85/100 000 in children under 16 years of age was estimated.(65). However, in this study only severe cases in immunocompetent children under 16 with no primary diseases were included. There were no death reports. There was no other data bank comparison and no capture- recapture was available. Therefore, another study was carried out from January 2003- December 2004.(36) Assuming that all hospitalisations caused by varicella cases under 16 years of age were documented by ESPED a rate of 3.6 Hospitalisations /100,000 person years was calculated (36). A number over 4 fold of their previous study. A comparison with Nordrhein-Westfalen data bank and using capture recapture method an incidence of 15.7 /100,000 person years (95% CI, 6.9 - 22.3) varicella zoster induced hospitalisations was estimated. The long confidence interval shows how uncertain this result is. Overall 2121 (95% CI, 1447 - 2795) hospital admissions in children under 16 in Germany could be estimated.(36) .

Epidemiological study by Wutzler et al (62), Wagenpfeil et al.(55) Benz et al. (5) based on a survey including 1334 cases, as already described in this paper, report 16.3% frequency of serious complicatios (considered by the interviewed physician) as severe courses. Most common complications for children younger than 12 years were bacterial superinfection, pneumonia, bronchitis, neurological complication and otitis media. For the older age group the most common complications were bacterial superinfection and lower respiratory tract infections. Most serious Varicella-related complications occurred in hospital admission of 5.7% of patients (62). Frequency of hospitalalisation for children< 12 was 5.9%.

A comparison of hospitalisation frequency rates with studies from other countries can be seen in (table 3).

Table 3. Frequency of complications in varicella cases (age group 0-14)

Wutzler et al (2002)(62)	Fornaro (1999) (29)	Choo et al. (1995)(14)	Lieu et al[a] (1994)(35)
5.7%	3.5%	2.05%	0.25%

[a] Only most serious complications were included

Generally the differences could mainly be due to different definitions of complication. However, the study in Germany obviously shows a much higher rate than other studies. This rate has been later used in almost all cost benefit analyses. The estimated rates of incidence of varicella induced complications in Germany lie between 0.85- 24.7 /100,000 person years. In other countries in Europe between 2 (Switzerland)- 10 (Scottland) /100,000 person years (49).

Cost-benefit analyses

To evaluate costs and benefits of routine varicella vaccination in German children different studies have been carried out to compare the cost effectiveness of three strategies: [1]- Vaccination of all around 15 month-old children ('children' strategy), [2] Vaccination of susceptible 12 year-olds (' adolescent' strategy), [3] A combination of strategy 1 and 2 ('children including catch-up' strategy). All identified studies adopted medical care payer point of view and societal perspective in the cost analyses. They all conducted an age-structured decision analytic model, and the incorporated varicella transmission model was similar to that adopted by Halloran et al.; in all studies direct and indirect costs were calculated. They all considered 5% discounting of costs. And sensitivity analyses were done.

In the first study by Beutels et al (7) Markov simulation (an age-structured decision analytic model) to calculate benefits and costs over a 70- year time period. Different data sources were used. They used epidemiological data from USA. Efficacy of vaccine was set at 86% and the coverage rate of measles in Germany (70%) was used. It was assumed that no adverse events occurred due to vaccination. The proportion of people initially completely protected by vaccine, who become partially protected if their immunity is not boosted was estimated to be 15% (mean, 20%; range: 5-60%), of note the long confidence interval. This estimate was drawn from the study by Halloran et al in 1994. The number of days for parents staying home was 2.6 days/varicella case. To estimate the proportion of physician visits in case of varicella disease they used data from a health and pharma market research. According to this survey almost 90% of the cases consult a doctor.(7) This is the data also used in future studies in Germany. One way sensitivity analysis was carried out for vaccine efficacy, treatment costs, costs of work loss, discount rate, costs of vaccine, determination of susceptibility, coverage, waning of immunity and an additional booster dose. The sources of costs, sensitive parameters of the model and the assumed vaccination rate of the analysis is shown in (table 4).

Table 4. Calculated costs and assumed coverage rate in cost benefit analyses by Beutels et al.

Study (ref)	Direct costs	Indirect costs	Sensitive Parameteres	Vaccination coverage (base case)
Beutels et al (7)	visits to the physician, medication, hospitalisation and follow-up both uncomplicated and complicated varicella cases vaccination costs	production losses incurred by parents in taking care of their children and work loss of employed adults.	costs of work loss vaccine efficacy coverage vaccine price treatment costs	70%

This model predicted 57% prevention of varicella infections in a cohort of 800000 neonates (384,620) following children vaccination, 37% prevention following adolescents strategy and 55% after a combination strategy. The number of deaths avoided would be 20%(3.9), 35%(4.2), 25%(4.2) respectively. Total net savings for a cohort of 800,000German neonates after implementation of children, adolescents and combination strategy were estimated at 161.3 million DM (~ €82.47 million), 21 million DM(~ €10.74 million) and 182.3 million DM(~ €91.35) respectively.(€1= DM1.95583)

The main shortcoming of this study was that it did not take into account that sickness funds in Germany reimburse 70% of the work loss costs of employed parents taking care of their children ('Kinderpflegekrankengeld', 'child care benefiets').

All later literature (4,5,30,55,62) includes this part of indirect costs in the calculations and report almost identical results.Of note, they were supported by the vaccine supplier in Germany. Wutzler et al (62), Banz et al (4,5), Wagenpfeil et al (55) mention using the age-structured decision analytic model, Economic Varicella Vaccination Tool for Analysis (EVITA)(6,27). Knuf et al only mention a computer simulation model. They all used epidemiological data from the cross sectional retrospective survey carried out earlier by Wutzler et al.(62) and report the same (sometimes rounded) figures as outcome. Sources of costs, sensitive parameters and the assumed coverage rate of the model are demonstrated in (table 5)

Table 5. Sources of costs, sensitive parameters and coverage rate used in model by Wutzler et al.

Study (ref)	Direct costs	Indirect costs	Sensitive Parameteres	Vaccination coverage (base case)
Wutzler et al. (5,30,55,62)	cost of the vaccine, administration costs, and costs for the management of vaccine complications. treatment costs for varicella and its sequelae.	work loss costs of employed parents taking care of their children paid by the insurance and the production losses; work loss of employed adults.	vaccination coverage, discount rate of health benefits, cost of work loss of parents, vaccine price, discount rate of costs, and daily charge of hospitalisation.	85%

Indirect costs (work loss) were calculated by adopting the human capital approach. The number of work day lost was based on information obtained from the epidemiological survey. For the societal perspective, cost per work day lost was derived from the average gross income. Variables which were changed in the worst and best case scenarios include: coverage rate, vaccine efficacy, waning rate, relative susceptibility, relative infectiousness, probability of physician contact in case of infection, varicella complications, vaccine price, hospital charges, cost of work day lost, discount rate costs, and discount rate benefits. The sensitivity analyses indicated that the findings are most sensitive to the following assumptions:

Changes in the vaccine price have greater impact on the children and combined vaccination strategies than on the adolescent vaccination strategy since only a small group of adolescents will receive vaccination. All other model variables, including vaccine efficacy and waning immunity, are significantly less sensitive. The outcomes of the model are outlined in table 4.a. and 4.b.

Table 4a. Potential clinical effects of the different varicella vaccination strategies compared to no vaccination (EVITA Model -base case assumption)

Average annual rates	Varicella cases	Total complications	Major complications requiring hospitalisation	Deaths
No vaccination	738,967	39,722	5,739	22
Vaccination at the age of 15 months	127,776	6,848	1,004	4
Vaccination of susceptible persons at the age of 11–12 years	702,151	37,651	5,302	20
Combination of both Vaccinations (children and adolescents)	121,623	6,511	937	4

Table 4b. Potential economic effects of the different vaccination strategies from the societal and health care payer's perspective (base case assumption) expressed as net average annual cost/savings (Mio Euro) (62) (5) (30)

	Children vaccination strategy		**Adolescents vaccination strategy**		**Combined vaccination strategy**	
	Societal perspective	**Payer's perspective**	**Societal perspective**	**Payer's perspective**	**Societal perspective**	**Payer's perspective**
Direct costs	+3.9	+4.3	+0.25	+0.38	+4.4	+4.7
Indirect costs	–55.2	–16.6	–8.43	–0.52	–57.4	–16.8
Total	–51.3	–12.3	–8.18	–0,14	–53.0	–12.0
Benefiet-cost ratio*	4.12	1.75	8.44	1.13	4.10	1.70

*Net savings due to vaccination (in terms of disease treatment costs avoided plus indirect cost savings) divided by the vaccination costs

From a purely economic point of view, the most efficient strategy is vaccinating susceptible adolescents (BCR= 8.4), because it is targeted at preventing more severe disease in older age groups and can prevent 8% of major complications(62). However, it is less attractive for the sickness funds and from the medical point of view since significantly fewer number of infections can be prevented and as a result the substantial indirect costs can not be avoided.

Table 5 outlines sthe costs considered, the sensitive parameters of the model and the assumed coverage rate in the cost-benefit analyses.

Later studies showed a return of investment for the insurance(BCR of 1.75) for the children base case vaccination program, whereas Beutels et al. (7) reported a BCR of 0.82.
From the viewpoint of the society, however, the two BCRs for routine childhood vaccination are similar (4.12 versus 4.60). The benefit cost ratio outcome of both studies are compared in (table 6).

Table 6. Comparison of projected benefit cost ratio by two simulations

	Children vaccination strategy		**Adolescents vaccination strategy**	
	Beutels et al.	**Wutzler et al.**	**Beutels et al.**	**Wutzler et al.**
Societal BCR*	**4.60**	**4.12**	**6.02**	**8.44**

Discussion

As with most universal mass vaccination programmes, childhood immunisation against VZV could have a negative impact should it be introduced without sufficient coverage to induce herd immunity . Low vaccine coverage can result in an increase in the average age of primary infection, with a concomitant increase in severity of varicella in adult age groups (2,25), and especially in pregnant women, where infection can have adverse sequelae for both the mother and unborn child.. Vaccination is only predicted to decrease morbidity in both adults and children at around 70% coverage (8). Since VZV vaccine is recommended to be administered together with MMR vaccine or a few weeks later (1), we can assume that the highest rate for Varicella vaccine coverage would be similar to that of MMR vaccine, i.e about 77% (CI 95%: 72-81%) in 19-39 month old children in Germany (33). However, this assumption will be subject to full improvision of the vaccine costs by the insurance funds. One year after the recommendation by STIKO, 14 of 20 Associations of CHI Physicians in different federal states in Germany accepted reimbursement of varicella vaccination costs. (43)
To achieve high coverage rates, it is of outmost importance that all insurance funds across the country reimburse the costs. Otherwise, considering the current price of €54.73/dose (22) even a 70% coverage rate would be unlikely. This factor even becomes more important when we consider the vaccine price increase of more than US$ 10 per dose (inflation adjusted) since 1995 in USA (current price US$ 52.25) (13,13); and there are already disussions about whether using two doses could increase protection against varicella.(41).

Should vaccine uptake be low, the resultant long-term epidemiological shift of disease to older age groups could result in increased morbidity, due to the higher risk of complications in adults.

As in the industrialised countries, the main objective of mass vaccination against chickenpox is to reduce burden of the disease, the consequences of the programme should be carefully evaluated and any probable risks, which could have devastating effects in future should be given enough attention.

If the experience from USA repeats itself in Germany, depending on the vaccine uptake , dramatic declines in varicella hospitalizations, ambulatory visits, and their associated expenditures may be expected in the coming years(64). Indeed, the cost-benefit analyses carried out in Germany report large net savings both for the health care payer and the society. However, the extent of savings would unlikely be as large as those projected by the authors. All these studies used the same estimated epidemiological data (rather high complications frequency in comparison with other countries, and the same assumptions. The 30 year period of projection also did not include the potential impact of the programme on zoster incidence in their calculations. (4, 5, 30, 55, 62) Of note, models that take such an impact into account estimate a rise in HZ incidence during a 50 year time span after implementation of mass vaccination (33, 24)

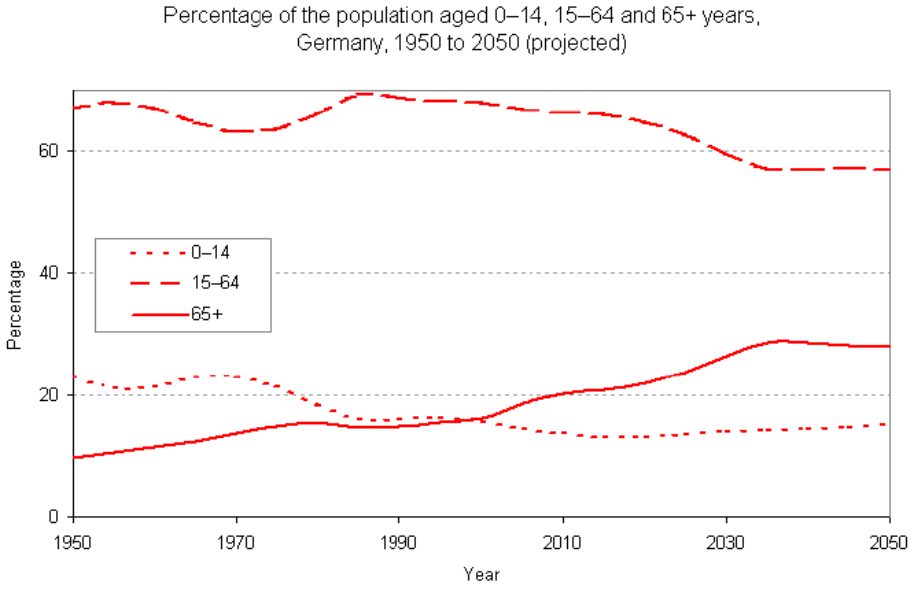
Cost-benefit analysis of universal varicella vaccination in the U.S. taking into account the related herpes-zoster epidemiology, estimates that universal varicella vaccination has the impact of an additional 14.6 million (42%) HZ cases among adults aged <50 years during a 50 year time span at a substantial cost burden of 4.1 billion US dollars or 80 million US dollars annually utilizing an estimated mean healthcare provider cost of 280 US dollars per HZ case.(24)

Although different studies have been carried out to find the exact relationship between varicella and herpes zoster and the process and factors influencing reactivation of the virus, our knowledge in this field is still remarkably limited (52). The possibility, that protection against zoster without the boosting effect of wild type virus decreases, can not be excluded. Neither can the theory that in the short to medium term mass varicella immunisation of children could cause a major epidemic of herpes-zoster, affecting more than 50% of those aged 10-44 years as a consequence of vaccination(33) Such an outcome could have devastating economic impact on a country like Germany where birth rate has dropped by 21% since 1990 (61) and the highest proportion of the population by 2050 is predicted to be

between 15-64 years old followed by the age group over 65 years(26.4%) (61). Diagram 4 shows the population trends projected for Germany by 2050(61).

Diagram 4 shows the population trends projected for Germany by 2050(61).

Diagram 4 . Population trends in Germany



Source: United Nations (2002).

Should this theory become reality, by the year 2030 around 15% of the whole population(10-44 year olds) would develop zoster. The only possibility to combat such an outcome would be implemeneting universal vaccination programmes against shingles at different ages and at different intervals. In their review of the mathematical modelling of universal vaccination literature considering the impact of the programme on HZ, Wagenpfeil et al admit that the risk of an increased herpes zoster in the initial period following vaccination exists, but they hope to avoid this increase by vaccination of the elderly. (51) The economic impact (both direct and indirect) of such mass vaccination has yet to be studied.

With implementation of a universal vaccination against chickenpox it is important that the age distribution of varicella disease is monitored, and this is best done through case-based surveillance of varicella. Initially, while disease incidence remains high, a well managed sentinel surveillance system could be an acceptable alternative (39). The surveillance system should be sensitive to zoster. There are already three varicella sentinel systems in Germany namely, the measles varicella sentinel (AGM/V) (a co-operation between Robert Koch Institute and vaccine suppliers), the German Paediatric Surveillance Unit (ESPED), Associations of CHI Physicians (KV) sentinel (in cooperation with Robert Koch Institute). (180)

Conclusion: The findings strongly support a re-evaluation of varicella vaccination in Germany, taking into consideration its impact on herpes-zoster. The risk may not be understimated. Immunisation against herpes zoster can be an attractive option in future, but it is still in its infancy and more information is required. In the meantime to monitor epidemiology of the disease and the vaccination impact planning a cohort prospective study is recommended.

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Eidesstattlich Erklärung

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