

**Hamburg University of Applied Sciences (HAW)**



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Master Course Public Health (MA)

**Routine Childhood Vaccination in Germany – Well-founded?**

**Master Thesis**

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**Matriculation Number: 1790174**

February 2006

## **Acknowledgements**

This work is based on an original abstract prepared by Dr. Alice Nennecke, Katja Schmidt and Mahdis Soltani during the Infectious Disease Epidemiology module in spring 2005. I should like to especially thank Dr. Nennecke for her support.

My thanks also go to Prof. Ralf Reintjes (Hamburg University of Applied Sciences) and Dr Richard Pebody (the Immunisation Department of the Communicable Disease Surveillance) for their willingness to be my advisors.

I am also grateful to my husband, Bahman Amiri, for his support and my dear parents for their encouragement.

## Table of Contents

1. Introduction .....	4
2. Varicella Disease .....	5
2.1. High Risk Groups .....	6
3. Herpes Zoster (HZ).....	6
4. Epidemiology .....	7
4.1. Disease incidence in Germany .....	7
4.2. Complications and hospital admissions in Germany.....	8
5. Prevention of varicella.....	10
5.1. Postexposure Prophylaxis in Immunocompromised Individuals .....	10
5.2. Varicella vaccine .....	10
6. Economic Considerations for a vaccination program .....	12
7. Public Perception and current vaccine uptake in Germany.....	13
8. Discussion.....	14
9. Appendices .....	15
Appendix 1. List Of Abbreviations .....	15
Appendix 2. List of used in Literatuer search & in Data Extraction.....	16
10. References .....	17
11. Article .....	25
Routine childhood immunisation in Germany – well- founded?	

## **1. Introduction**

Varicella-zoster virus (VZV) causes two distinct clinical diseases. Primary infection causes varicella or chickenpox mostly in children usually affecting 90% of them before adolescence.(89) Though usually mildly proceeding severe complications may occur, particularly among pregnant women, neonates, adults and the Immunocompromised. It is presumed, based on autopsy studies, that latent VZV infection develops in the sensory ganglia of the majority of individuals following natural varicella (61,76) ; later in life 10-20% are afflicted by herpes zoster (Shingles) through reactivation of the dormant varicella zoster virus. The likelihood that every child will contract varicella, combined with a socioeconomic structure that implies high indirect costs for each case, make varicella relatively important in industrialized countries with temperate climates. Routine childhood vaccination against this disease is estimated to be cost-effective in such areas. According to World Health Organisation (WHO), routine childhood immunization against varicella may be considered in countries where this disease is a relatively important public health and socioeconomic problem, where the vaccine is affordable, and where high (85%–90%) and sustained vaccine coverage can be achieved (Childhood immunization with lower coverage could theoretically shift the epidemiology of the disease and increase the number of severe cases in older children and adults (120). Varicella vaccination has been standard for all children and young people in the United States since 1995, with good results (43,47). With regard to an estimated over 750 000 varicella cases annually and consequent societal costs the Standing Committee on Vaccination at the Robert Koch Institute (STIKO) in Germany recommended universal childhood immunisation against varicella in July 2004(89). Making Germany the first country in the European Union to do so (34). The vaccination should preferably be carried out at the age of 11- 14 months. Unvaccinated children and adolescents of 9- 17 years of age with no history of natural varicella disease should be vaccinated as soon as possible. As the disease is more severe and results in higher complication rates in this age group. (89) Prior to the current recommendation, varicella vaccination was only recommended for particular risk groups (and their contacts), and for young people who had not had varicella. These recommendations were often not followed (34). 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 certain issues of controversy which should be considered. Potential harm that may occur as a result of

vaccination includes 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 (95). Furthermore, introducing universal vaccination for children necessitates disease surveillance and modifications of the recommendation as needed. The epidemiology of herpes zoster must be tracked as well as varicella disease trends. The objective of this paper is to review the universal varicella vaccination recommendation in Germany and the underlying data.

## **2. Varicella Disease**

In healthy people, varicella also known as chickenpox is usually a mild self limiting illness, characterised by low grade fever, malaise, and a generalised, itchy, vesicular rash. It is caused by exposure to varicella zoster virus. Varicella virus, which is a DNA virus a member of the herpes virus group. Like other herpes viruses, VZV has the capacity to remain latent in the body after the primary (first) infection (115).

Second attacks of varicella are unusual in otherwise healthy individuals, although they are recognized to occur (27, 49). One estimate is that 1 in 500 history-positive persons with a household exposure to varicella will experience a second attack (49).

In temperate climates, 95% of varicella cases occur among persons less than 20 years of age. Seropositivity is lower in adults from tropical and subtropical areas. Seronegativity in adults may be increasing in temperate populations, as shown by a significant upward trend in age distribution of chickenpox cases in England and Wales, and increasing varicella susceptibility in young US adults (95).

Varicella is highly contagious and is transmitted both by droplet infection and by direct contact. It is thought to enter the respiratory tract as an airborne virus (115,45). The incubation period averages 14-16 days; it can range from 10-21 days. The period of infectiousness is estimated to begin 1-2 days before the onset of rash and ends when the lesions are crusted, which is 4-5 days later. There is immunologic evidence to suggest that subclinical reinfection with VZV is common, although it is unknown what role reinfection plays in the maintenance of protective antibody levels (115).

Acute varicella is generally mild, but may be associated with complications. The severity of natural varicella in immunocompetent individuals has been the subject of controversy for a number of years. However, at least 1% of children under 15 years experience a

complication (96) the infection can lead to serious complications, such as Staphylococcus aureus infections, otitis media, endocarditis, pneumonia, and rare central nervous system (CNS) events like cerebellar ataxia and encephalitis. The most significant complications of varicella include secondary bacterial infections of skin lesions, dehydration, pneumonia, and central nervous system involvement. Reye's syndrome was at one time a dreaded complication of varicella, but it disappeared with the cessation of the use of aspirin as a childhood antipyretic agent.(49, 72, 95)

### **2.1. High Risk Groups**

Varicella is 25 times more likely to be serious in adults than in children. Immunocompromised individuals and the newborn are also at high risk of developing severe or fatal varicella. A disabling but rare congenital varicella syndrome (consisting of skin scarring, limb abnormalities, brain damage, and ocular malformations) affects up to 2% of offspring born to women who contract chickenpox in the first or second trimester of pregnancy (27, 49). Varicella infection in the newborn varies in severity according to the timing of infection. When maternal infection occurs from 3 weeks to 5 days before delivery neonates have mild varicella disease because of protective maternal antibodies. However, if maternal varicella occurs between 5 days before to 2 days after delivery, and the virus is transmitted across the placenta, potentially severe neonatal varicella may occur, since there is no protective effect of maternal antibody. In the latter, disease develops at between 5 and 10 days of age. A case fatality rate of 20-30 per cent has been reported (49). Seronegative pregnant women are an additional high-risk group for varicella complications. The most common complication in USA is varicella pneumonia, which occurs in 1-5 per 10,000 cases (49). Mortality is estimated to be as high as 40% in pregnant women without treatment (49). Congenital varicella syndrome occurs as a result of vertical transmission in the first and early part of the second trimester, with an incidence of 0.4% and 2% respectively (27).

### **3. Herpes Zoster (HZ)**

Herpes zoster (shingles), a painful, vesicular rash of skin occurs with reactivation of the virus in approximately 15% of the population. It is manifested by a localized, unilateral, and painful vesicular rash. In itself, this represents considerable morbidity. Zoster may also

be complicated some weeks later by postherpetic neuralgia, an extremely painful condition for which there is little effective treatment (49). The likelihood of developing herpes zoster increases with advancing age. The incidence is approximately 74 per 100 000 children aged under 10 years, 300 per 100 000 adults aged 35-44 years, and 1200 per 100 000 adults over 75 years. (95)

#### **4. Epidemiology**

In the prevaccine era there were about 4 million cases of varicella annually in the United States, with 100 deaths (mostly in otherwise healthy individuals and despite the availability of antiviral therapy) and 11,000 hospitalizations. Most VZV infection results in a clinical illness, but about 5% of primary infections are subclinical.(49)

10-50% of all children will visit a physician with an infection (95). The mortality rate of varicella in children under 14 years in the United States is estimated at 2 per 100 000 cases, and 90% of these have no risk factors for severe disease. Adults experience only 5% of all varicella cases, but experience more severe disease (hospitalisations 18 per 1000) and deaths (50 per 100 000).(95)

Zoster, on the other hand is mainly a disease of individuals over the age of 50 years and immunocompromised persons. Reactivation of latent varicella zoster virus as herpes zoster is thought to result from waning of specific cell-mediated immunity (CMI), but little is known about its determinants in individuals with no underlying immunosuppression. A systematic review of studies of zoster epidemiology in adults reports an annual zoster incidence from 3.6-14.2/10000 in the oldest individuals. Risk factors identified that could explain this variation include age, sex, ethnicity, genetic susceptibility, exogenous boosting of immunity from varicella contacts, underlying cell-mediated immune disorders, mechanical trauma, psychological stress, and immunotoxin exposure in the oldest individuals. Information about risk factors for zoster is still limited. (105)

##### **4.1. Disease incidence in Germany**

Chickenpox is not a notifiable disease in Germany. A few studies have been carried out to produce estimations on seroprevalence and epidemiological data the results of which are outlined in (table 1). More information is provided in the article at the end of this paper.

**Table 1.** Seroprevalence of Varicella disease in the German population under 20 years of age indicated by different studies (All figures rounded to one digit)

Age	Schneweis et al. (98) (1985, n=380)*	Buxbaum et al. (18) (2001, n=2.291)*	Wutzler et al. (123) (2001, n= 4602)*	Wutzler et al. (122) (2002, n=1334)**
Under 5	33%	26%	63%	59%
Under 10	65%	68%	92%	88%
Under 15	80%	90%	97%	91%
Under 20	90%			92%

\*Number of serums tested.

\*\* Number of reported chickenpox cases

#### 4.2. Complications and hospital admissions in Germany

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.(28) The related hospitalisation data caused by varicella and zoster in all age groups can be seen in the table below (table 2)(28):

**Table 2.a.** B01 Varicella [chickenpox] and B02 Zoster [herpes zoster]

Year	Hospitalisations Varicella	Hospitalisations Zoster	Deaths Varicella	Deaths Zoster
2003	1,969	12,833	7	113
2002	1,806	12,579	9	79
2001	1,829	12,195	8	67
2000	1,957	11,438	4	64

\*ICD stands for "International Statistical Classification of Diseases and Related Health Problems", 10 refers to 10. Revision of classification.

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 related data has been outlined in (Table 2.b).

**Table 2.b.** Hospitalised chickenpox cases under 15 years of age and their average number of bed stay. Germany 2000-2003(ICD-10, B01)

	2000	2001	2002	2003
Cases <sup>a</sup>	1,323	1,128	1,161	1,239
Day of stay <sup>b</sup>	5	5.3	5	4.9

<sup>a</sup> Number of hospital admissions

<sup>b</sup> Average day of bed stay

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, established in 1992 to study the epidemiology of rare childhood diseases. A report card is mailed each month to all 485 pediatric department heads in Germany to determine whether a patient who was up to 16 years of age and had a defined rare illness was hospitalized. The system was used to provide data on varicella induced hospitalisations in Germany. They estimated a crude incidence of severe chickenpox complications of 0.85/100 000 (125). In a later study ESPED reported an incidence of 15.7/ 100000 person years (75). (Please see the attached article at the end of this paper)

In the epidemiological study by Wutzler et al (122), Wagenpfeil et al.(109), Benz et al. (5) 16.3% of varicella cases were considered by the physician as severe courses. Out of 92 identified complications 16 were identified as coincident with varicella. The age adjusted hospitalisation rate was 5.7%.

For more information on disease burden in Germany, please see the attached article to the end of this paper.

## **5. Prevention of varicella**

### **5.1. Postexposure Prophylaxis in Immunocompromised Individuals**

Administered in the form of varicella-zoster immune globulin (VZIG), passive immunization is useful in preventing or ameliorating clinical varicella in VZV-exposed persons at high risk of severe chickenpox (whereas prompt administration of live attenuated vaccine is appropriate postexposure prophylaxis in susceptible immunocompetent individuals). The main use of VZIG, therefore, has been in immunocompromised children (49).

### **5.2. Varicella vaccine**

Oka-vaccine is a live attenuated vaccine derived from a wild-type virus. The Oka varicella vaccines currently licensed in Germany are Varicella-GSK, Varilrix (both to GlaxoSmithKline GmbH & Co. KG) and Varivax (to Sanofi Pasteur MSD GmbH, 61981 Leimen). The vaccine is currently administered as a single vaccine.(84) Many different doses of varicella vaccine have been studied in various clinical trials. Two double-blind placebo-controlled studies of varicella vaccine (one with Merck vaccine, and one with vaccine prepared by GSK) together involving about 1,500 children showed that high-titer vaccine (10,000 to 17,000 PFU) was between 88 and 98% protective against varicella (107, 112). Lower doses (<1,000 PFU) gave reduced rates of protection (107, 112). The currently licensed Merck vaccine contains about 3,000 PFU per dose, and the GSK vaccine contains about 10,000 PFU at the time of release, which, prior to the expiration date, falls to about 3,000 PFU (49).The Merck vaccine is lyophilized and frozen, while the GSK product is lyophilized and refrigerated. 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%) (49).

To reduce the frequency of breakthrough infections of varicella, this vaccine is advised to be given in a 2-dosis schedule in the second year of life (i.e at 12-14 month, and a second dose 6-8 weeks later). This schedule is equal to the current MMR schedule of Germany.

Live vaccines against Measles, Mumps and Rubella (MMR) in combination with the Varicella (i.e.MMRV) have also been tested for effectiveness in clinical studies. Administration of 2 doses of the combined MMRV vaccine appear to be as immunogenic and well-tolerated as separate injections of MMR and varicella vaccine given at 12-15 months (63, 103, 111). However, there are debates on safety of MMR vaccine and in their systematic review of studies of MMR vaccine safety Demicheli et al. report inadequate

design and reporting of safety outcomes in MMR vaccine studies, both pre- and post-marketing. The evidence of adverse events following immunisation with MMR cannot be separated from its role in preventing the target diseases (24).

Contraindications to varicella vaccine mainly include: (a) anaphylaxis with a previous dose of varicella vaccine, (b) a history of hypersensitivity to any vaccine component (c) advanced HIV infection and Aids, (d) steroid treatment Prednisone:  $\geq 2\text{mg/Kg}$  Weight /Day or  $\geq 20\text{mg/day}$  more than 14 days, (e) pregnancy (after the second dose pregnancy should be avoided), (f) treatment with Immunglobulinen or blood products (at least 5 months abstention), (g) severe acute diseases.

An overview of the studies addressing efficacy and effectiveness of the vaccine is provided in (table 4).

**Table 4.** Studies addressing vaccine efficacy and effectiveness

Study (year) (ref)	Study Design	Number of vaccinees*	Number of unvaccinated	Number of doses	Duration of follow up	Efficacy/effectiveness (range)** against	
						All forms of varicella	Moderate-severe varicella
Weibel et al. (1984) (112) Kuter et al. (1991) (67)	Double blind, placebo-controlled trial	468	446	1	2-7 years	98% <sup>a</sup>	100%
Varis and Vesikari (1996) (107)		325	155	1	29 Months	72% <sup>b</sup>	
White et al (1991) (49)	Un-controlled Clinical trial	82 <sup>c</sup>	HPC <sup>d</sup>	1	1 year	86%	100%
Johnson et al. (1997) (59)		281	HPC <sup>d</sup>	1	6-10 years	66-81%	
Takayama et al (1997) (49)		64-159 <sup>e</sup>	HPC <sup>d</sup>	1	6-8 years	43%	
Kuter et al (2004) (49)		618-1104 <sup>e/</sup> 617-1017 <sup>e</sup>	HPC <sup>d</sup>	1 / 2	10 years	94% <sup>f</sup> (93-96)/ 98% <sup>g</sup> (97-99)	100%  100%
Vazquez et al. (2001 and 2004) (108,109)	Case control	592	416	1	8 years	87% <sup>h</sup> (81-91)	98% (93-99)
Clements et al. (1999) (23)	Dynamic cohort	4,658 person-months	10,274 person-months	1		83% (69-91)	100%
Izurrieta et al. (1997) (58)	Retrospective	66	82	1		86 % (73-92)	100% (96-100)

\* Only those seronegative at the time of vaccination are considered.

\*\* 95% confidence interval

<sup>a</sup> 100% in the first year, and 96% in the second year.

<sup>b</sup> Two different titers of vaccine were compared, the lower (630 to 1,260 PFU) being approximately 55% effective and the higher (10,000 to 15,850 PFU) being about 88% effective in protecting from varicella.

<sup>c</sup> Efficacy was measured against varicella following household exposure

<sup>d</sup> Historical Population Controls.

<sup>e</sup> Subjects were monitored for 10 years, with a gradual reduction in sample size.

<sup>f</sup> 90% (84% to 98%) effective against household exposure.

<sup>g</sup> 96% (92% to 100%) effective against household exposure.

<sup>h</sup> When analyzed by time since vaccination, population efficacy was 97% in the first year, falling to 84% thereafter.

## **6. Economic Considerations for a vaccination program**

Costs and benefits of three different routine varicella immunisation strategies should be evaluated: 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).

An economic analysis of the benefit of vaccination is based on four parameters:

Direct cost of the vaccination program: The cost of the vaccine plays a key role. Vaccine costs can theoretically be reduced by achieving high coverage (allowing volume-based reduction in cost/dose). Associated costs can be reduced by incorporating the vaccine into other mandatory vaccines (e.g. adding varicella to the MMR vaccine).

Direct savings permitted by the vaccination program. Direct savings owed to lower incidence of the disease, which in turn lowers the cost of treatment. The result is fewer outpatient visits, hospitalizations and medication. Estimates of direct savings vary greatly among countries, with the general rule that higher health care costs translate into higher direct savings.

Indirect savings produced by the vaccination program refer to the implicit cost of absence from work to care for infected children and the estimated costs of mortality and morbidity. In general, indirect economic costs will be higher for more developed nations, owing to the higher productivity per capita. However, from a social perspective, the lost income may be more critical to the welfare of families in less developed countries.

Willingness of individuals to pay for protection against the normal sequelae of the disease, measured in currency.

These parameters can be used to calculate economic benefit from several different perspectives. Benefit to the health care payer (i.e. insurance companies, the government, or individuals) is equal to direct savings minus direct costs. The benefit to society, which includes the protection of immunocompromised or otherwise susceptible individuals, is equal to direct savings plus indirect savings minus direct costs. Finally, the benefit to an

individual consumer is equal to their willingness to pay (assumed ‘market’ value of vaccination) minus direct costs. All future cash flows must be discounted.

These measures are summarized in the (table 5):

**Table 5.** Calculation formula for benefit recipients

Payer Benefit	Direct Savings – Direct Costs
Society Benefit	Direct Savings + Indirect Savings – Direct Costs
Consumer (individual) Benefit	Willingness to Pay – Direct Costs

While some studies do imply a societal benefit resulting from mass vaccination (122,123), other recent studies have raised concerns that may negate this perceived economic value. Some studies have been conducted using an age-structured dynamic transmission model to simulate the effects of vaccination based on studies which show that resistance to zoster may be diminished in vaccinated individuals (vs. individuals who have contracted chickenpox) These studies show that vaccination results in a net loss to society, owing to higher incidence of zoster among adults. The authors also raise the concern that, as chickenpox cases diminish, natural immunity ‘boosters’ may become depleted, resulting in even higher zoster incidence amongst adults. This would further diminish the benefit from vaccination.(6,10,11,13,33)

## **7. Public Perception and current vaccine uptake in Germany**

A successful vaccination programme against highly contagious diseases must reach high rates of coverage. Vaccinations in Germany are mainly performed by paediatricians in their consulting rooms, whereby 90 percent of childhood vaccinations are administered by paediatricians. Vaccination is an individual decision (parents of children) after consultations with the physician. A recent study of vaccination rates in Germany indicates that only 59% of recommended vaccinations are performed.(30) For instance, in the case of measles only in 30% of school children the second dosis of the vaccine has been administered.(30) The MMR vaccine shows immunisation rates of about 70% at school entrance age (97) and 77% (CI 95%: 72-81%) in 19-39 month old children(97). In adolescents vaccination rates against Hepatitis B and whooping cough are even lower than 30% (97). A survey to find the reason behind low immunisation rates in Germany reports that over 50% of parents admit to not having sufficient information and about 10% are anti-vaccination (30). In addition, there seems to be a vaccination fatigue or fatigue in the physicians to motivate people to vaccinate (55). Generally, to reach high coverage rates

and reduce costs in the interest of the society, the physicians are recommended not to give information on the vaccine risks directly. They should either leave this task to their nonmedical employees or provide related leaflets (17). Which could be one explanation for lack of knowledge in the general public about vaccines and could eventually result in lack of confidence in the health care providers. Indeed, the rate of childhood vaccination refusal by parents has been increasing in the United States. A case control study in four states to determine why parents claim nonmedical exemptions to school immunization requirements show that the most common vaccine not received is varicella (53.1%), and the most common reason stated was concern that the vaccines might cause harm. These parents showed less confidence in the medical, public health, and government sources for vaccine information.(93).

## **8. Discussion**

Initially vaccines were developed to protect against life-threatening and disabling diseases (e.g. rabies, diphtheria), to eradicate sweeping outbreaks of serious diseases (e.g. paralytic poliomyelitis, smallpox), and to prevent diseases in a vulnerable population by the immunization of surrogates (e.g. vaccination of women at child bearing age against rubella to prevent congenital rubella syndrome). Now there is a new motive: prevention of less serious infectious diseases as a measure to improve quality of life. Although varicella infections can be life-threatening, most cases are self-limited and have no significant sequelae. Immunisation is more likely to improve quality of life than to save lives. Therefore, the immunisation programme potential economic savings should be carefully evaluated considering any potential risk(s).

## **9. Appendices**

### **Appendix 1. List Of Abbreviations**

AGM/V= Arbeitsgemeinschaft Masern und Varizellen ( Measles & Varicella Sentinel)

EU = European Union

€ = Euro

DM = Deutsche Mark

CASP = Critical Appraisal Skills Programme

CDC = Center for Disease Control

CI = 95% Confidence Interval

CMI = Cell Mediated Immunity

ESPED = Erhebungseinheit für seltene pädiatrische Erkrankungen in Deutschland

EVITA = Economic Varicella Vaccination Tool for Analysis

HZ= Herpes Zoster

KV = Kassenärztlichen Vereinigungen

PFU = plaque-forming unit

STIKO = Ständige Impfkommision am Robert-Koch Institut

RKI = Robert Koch Institut

MMR = Measles-Mumps-Rubella

US\$ = American Dollar

US = USA = United States of America

VAERS = Vaccine Adverse Event Reporting System

VZIG = Varicella-zoster immune globulin

VZV = Varicella Zoster Virus

## **Appendix 2. List of terms used in Literature search & in Data Extraction**

### **List of Terms Used in Literature Search**

Methodological search terms used in combination included:

varicella, varicella vaccinerandom allocation, placebo, double-blind method, comparative study, epidemiologic methods, research design, clinical trials, controlled clinical trials, meta-analysis, review, prospective studies, surveillance, post-licensor, cost-effectiveness, modelling, impact on herpes zoster, breakthrough, safety, vaccine effectiveness, adverse reactions, contraindication, transmission from vaccinated, shift in age, pregnant, children, adult, cost –effectiveness, herpes zoster, herpes zoster vaccine, cost-effectiveness, cost-utility, economic, USA, Germany, Europe.

Varizellen, Impfung, Empfehlung, MMR Raten, Masern Raten, Kostenübernahme, Sentinel, Seroprevalenz

### **Data extraction**

***Vaccine effectiveness and safety:*** number of vaccinees, number of unvaccinated, the studied population, number of doses, duration of follow up, efficacy and/or effectiveness were extracted from the related epidemiological studies or surveillance reports, adverse events, dosage, under this title other related factors were also considered and looked for. Outcome measures that included household contact and varicella transmission, outbreaks, boosting of immunity, herd immunity.

***Disease burden:*** Seroprevalence data regarding year, number of samples tested, the percentage of positive results in different age groups or in case of epidemiological studies the number of population studied and methods used were extracted from different studies and the results were compared within Germany and with international studies.

To find data on varicella complication data extracted included: number of hospitalisations Varicella, number of hospitalisations Zoster, average bed stay days, Rate of complication incidence and hospitalisation, kind and frequency of complications resulting in hospital admission. Data were compared within Germany and in the international context.



**Cost-benefit analysis:** Data looked for included: study design, epidemiological data, economic data and model characteristics, perspectives considered, duration of modelling, sensitivity analysis and the changed parameters, results of sensitivity analysis, net costs and savings, benefit cost ratio, impact on herpes zoster epidemiology.

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