ECDC **GUIDANCE**

Varicella vaccination in the European Union

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Contents

Abbreviations

ALL	Acute lymphoblastic leukaemia
BV	Breakthrough varicella
CDC	United States Centers for Disease Control and Prevention
CMI	Cellular mediated immunity
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EU/EEA	Countries that are members of the European Union plus Lichtenstein, Norway and Iceland
GMC	Geometric mean concentrations
GP	General practitioners
HZ	Herpes zoster
IgG	Immunoglobulin G
MMR	Measles – mumps – rubella
MMRV	Measles – mumps – rubella – varicella
OCS	Office of the Chief Scientist
SRS	Surveillance and Response Support Unit, ECDC
VPD	Vaccine-preventable diseases
VZV	Varicella zoster virus
WHO	World Health Organization

Country abbreviations

BG	Bulgaria
CZ	Czech Republic
DK	Denmark
DE	Germany
EE	Estonia
IE	Ireland
EL	Greece
ES	Spain
FR	France
HR	Croatia
IT	Italy
CY	Cyprus
LV	Latvia
LT	Lithuania
LU	Luxembourg
HU	Hungary
MT	Malta
NL	Netherlands
AT	Austria
PL	Poland
PT	Portugal
RO	Romania
SI	Slovenia
SK	Slovakia
FI	Finland
SE	Sweden
UK	United Kingdom

Preface

The Vaccine-Preventable Diseases Programme of the European Centre for Disease Prevention and Control (ECDC) has set up a working group to provide guidance to the European Union Member States on the potential introduction of varicella vaccination.

The aim of the final report of the working group is to support EU Member States in their national decision-making process with regard to childhood varicella vaccination.

To assist the working group in developing an evidence-based guidance document, a systematic review of the best available evidence was commissioned along with work on varicella modelling. The systematic review was produced by Pallas Health Research and Consultancy. Additional modelling outputs were produced through a Framework Partnership Agreement (ECDC Grant 2009/002) with Pisa University.

1 Executive summary

1.1 Main findings

Varicella is a common, highly communicable disease, caused by the varicella zoster virus (VZV).

In the EU/EEA, antibodies to VZV are generally acquired below 10 years of age. By the time they reach young adulthood, the majority of individuals are seropositive.

However, in some countries, antibodies are acquired at an earlier age and it has been observed overall that seroprevalence is marginally lower among children in southern and eastern European countries than in the countries of northern and western Europe. This might be attributed to variations in the use of day-care and pre-school facilities and different social contacts.

Most neonates are seropositive at birth, in general due to the presence of passively-acquired maternal antibodies.

In the absence of vaccination, the annual number of varicella cases in a given country is close to the country's birth cohort, with 52–78% of the incident cases occurring in children under six years and 89–95.9% of the cases before 12 years of age.

Differences in healthcare systems and study methods make it difficult to compare healthcare use due to varicella in the EU/EEA. Additionally, hospitalisations will depend on the age of infection (which differs between the countries).

Though most persons with varicella make full recoveries, 2–6% of varicella cases attending a general practice are estimated to develop complications. The most frequent complications are skin and soft tissue superinfections, followed by neurological and pulmonary complications. Long-term sequelae have been reported in 0.4 to 3.1% of patients hospitalised for varicella infections. The risk of severe varicella is higher in immunocompromised individuals, infants and adults. Nevertheless, most complications, hospitalisations and deaths due to varicella occur in children who are immunologically healthy with no underlying medical conditions.

There is growing evidence that monovalent and combined varicella vaccines are highly immunogenic, efficacious and safe in preventing varicella disease. Efficacy is very high against severe varicella and lower against less severe varicella after a single dose of varicella vaccine. High efficacy has been observed with two doses in preventing disease of any severity. The most common adverse reactions following varicella vaccine are local reactions, such as pain and erythema. An increased risk of febrile seizures after the first dose of a combined MMRV (measles, mumps, rubella and varicella) vaccine at age 12–23 months compared to separate MMR and V administration has been reported, however, MMRV may help achieve higher vaccination coverage.

Varicella vaccine effectiveness has been estimated around 85% and breakthrough varicella (BV) cases do occur, mainly after one-dose vaccination. BV is milder, with fewer skin lesions, shorter duration of the rash and fewer reported complications. No conclusive evidence is available for different risk factors of vaccine failure; however, effectiveness of one dose points to some primary vaccine failure. Recent studies have shown no consistent evidence of secondary varicella failure.

The experience of outbreaks in vaccinated populations has shown that varicella vaccination decreases the number, size and duration of varicella outbreaks and that decreases were greater with a two-dose schedule.

Varicella vaccine recommendations in the EU/EEA are heterogeneous, with only six countries where varicella vaccination is universally recommended for children at national level (CY, DE, EL, LV, LU) and two countries at regional level (ES, IT). Seventeen countries recommended nationwide vaccination for susceptible teenagers and/or susceptible (medical or occupational) risk groups only.

Surveillance from countries that have implemented universal varicella vaccination in children have shown a rapid reduction in the incidence of varicella cases, varicella complications, hospitalisation rates and deaths in all age groups, both in vaccinated and in unvaccinated individuals. A relative increase in the age of infection has also been reported in some studies, due to the decrease in the number of cases in younger age groups.

To date, there is no clear evidence of the overall influence of varicella vaccination on herpes zoster (HZ) epidemiology. Surveillance studies have demonstrated a decline in HZ incidence among varicella-vaccinated children, but have also suggested a trend of increasing HZ incidence in older unvaccinated children. Additionally, two studies, including a cohort study following vaccinated children in the USA for 14 years, found no increase in HZ incidence following introduction of varicella vaccination in the general population and vaccinated children, respectively. On the other hand, some studies found an increase, which, however, was reported even before the implementation of the vaccination programme. Therefore the potential influence of the vaccine on HZ incidence is difficult to interpret. Monitoring the impact of varicella vaccine on HZ, including in unvaccinated groups, remains a priority.

Mathematical modelling studies predict a decrease in the incidence of varicella following the introduction of the vaccine, which is in line with the published evidence.

Most models, which assume the exogenous boosting theory, suggest that if exposure to varicella boosts immunity to HZ, mass infant immunisation may result in an increase in HZ in the medium-long term (30–75 years after the introduction of a vaccine programme) and a decrease afterwards. One recently published modelling study predicts that this medium-term increase in HZ may vary according to the immunity boosting force.

Health economic evaluations on varicella vaccination programmes show that the majority of savings occur as a result of preventing indirect societal costs. When incorporating the potential effect of boosting immunity to HZ, models are not cost-effective in the medium term. Targeted strategies (such as vaccination of susceptible adolescents, healthcare workers, transplant recipients and young migrants) appear to be cost-effective.

The surveillance systems for varicella and HZ in the EU/EEA are highly heterogeneous and in several countries there were no systems in place at all. Most countries have no surveillance system for HZ. Continuous surveillance of varicella and HZ is needed in order to assess the impact of varicella vaccination on both diseases. The key elements to monitor should be age-specific disease incidence and disease severity of varicella and HZ, vaccine coverage and occurrence of adverse events. Additional years of surveillance will be needed to fully describe the impact of the programmes currently running.

1.2 Main conclusions

There is growing evidence that varicella vaccines are highly immunogenic, efficacious and safe in preventing varicella disease. Evidence from countries that have implemented universal varicella vaccination of infants demonstrates a significant and sustained decrease in the burden of varicella, with no apparent increases in HZ in vaccinated populations to date.

When considering the introduction of a vaccination programme, countries should assess their individual epidemiological and socioeconomic situation as well as the capacity to achieve high vaccination coverage.

Monitoring the impact of varicella vaccination programmes on the epidemiology of HZ remains an important priority. Good surveillance systems that provide knowledge of historical trends in HZ incidence and post-herpetic neuralgia are of utmost importance. Additionally, there is a need to increase our understanding of the immunological mechanisms behind HZ development.

1.3 Areas for further research

The following areas will benefit from further research; they are also the most likely areas to influence decisions on the implementation of varicella vaccination programmes in EU/EEA countries:

- Duration of vaccine-induced immunity beyond 14 years
- Optimal time for a second dose
- Potential need for further doses later in life
- Impact of vaccine coverage on the long-term epidemiology (i.e. shift to older ages) of the disease
- Severity of BV with an increase in time since vaccination (including BV outcomes in previously vaccinated pregnant women)
- Risk of an increased number of complications due to varicella following shifts in the mean age of infection after vaccine introduction (including congenital and maternal varicella)
- Immunological mechanisms for HZ development
- Impact of varicella vaccination on HZ incidence, especially in unvaccinated individuals

2 Methods

The objective of this guidance is to synthesise the available evidence on varicella and varicella vaccination in the EU/EEA.

A systematic review of the disease burden of varicella and childhood varicella vaccination in Europe was commissioned [1].The systematic review is available upon request from vpd@ecdc.europa.eu.

As regards the burden of varicella, only articles referring to the EU/EEA were included. As a result of this geographical limitation, some well-established information about the epidemiology of varicella, such as that on the increased risk of severe disease among adolescents and adults, was not adequately captured. Data on disease severity in the EU/EEA was mainly limited to numbers of hospitalisations. Rates on varicella consultation and hospitalisation and case-fatality rates are limited to the UK.

As the systematic review included references up to September 2010, one author updated the sections 'Burden of varicella in Europe' and 'Public health impact of varicella vaccination in the EU/EEA' for the period 1 September 2010 to 6 July 2012, with the same search term string used in the Pallas review, but only in PubMed and Embase databases. The results of this update are presented in the annex.

Additionally, ECDC commissioned work on varicella mathematical modelling to provide modelling input and advice on the effects of a VZV vaccination programme.

The project included a review of the existing models and the different contact patterns in the EU/EEA, as well as the production of new models, taking into account the reviewed papers and contact patterns. These reports were delivered to ECDC in March 2012 and included in the review. They have been published in peer review journals [2-4].

The expert panel, coordinated by ECDC, developed all the chapters of this guidance based on the systematic review and results of modelling work. For the guidance document, the panel took into account selected recent publications not included in the systematic review or its update (after 6 July 2012). When this is the case, the name and year of the reference is stated in the text.

3 Background on varicella

Varicella is a common disease caused by the varicella zoster virus (VZV), which typically affects children aged 2–8 years.

After the primary infection, VZV has the capacity to persist as a latent infection in the sensory nerve ganglia. Primary infection with VZV results in varicella (chickenpox) and reactivation of VZV causes herpes zoster (HZ) (shingles)[5].

Factors associated with VZV reactivation include aging, immunosuppression, intrauterine exposure to VZV, and having had varicella in the first year of life [5-8]; however, the immunological mechanism that controls latency of VZV is not well understood. Cell-mediated immunity (CMI) appears to play an important role in the host immune response to VZV [9,10]. Several studies show that CMI may be necessary to maintain latency; VZV reactivation and development of HZ may occur as CMI declines with advancing age or other immune-suppressing factors [9,11-15]. Intrauterine exposure during late pregnancy and or early postnatal varicella would predispose for HZ because infants in these situations have not developed adequate VZV-specific CMI [6,16,17].

Additionally, CMI may be boosted periodically by re-exposure to exogenous virus from individuals infected with varicella or HZ or by endogenous subclinical reactivation of the latent virus [18].

Scientific support for the role of external viral exposure to VZV immunity is inconclusive, with both supportive [19-22] and non-supportive [23,24] evidence that re-exposure to VZV may be protective against HZ development by boosting CMI. Ogunjimi et al. 2013 [25] recently published a systematic review of the literature concluding that exogenous boosting for VZV seems to exist, although it remains unknown to what extent it affects HZ incidence.

Endogenous subclinical reactivation, or endogenous boosting, may play a role in maintaining VZV-specific immunity and long-term protection against varicella, even though data are scarce; some studies have been published, both following natural varicella and varicella vaccination, showing subclinical VZV viremia or salivary shedding in immunocompromised individuals [26,27], hospitalised immunocompetent children [28] and astronauts [29], probably in response to stress.

Varicella is highly communicable and endemic to all countries worldwide. In temperate climates and in the absence of varicella vaccination, at least 90% of the population develop the disease by age 15 years and 95% by the time they reach young adulthood. Infection from primary varicella usually confers lifetime immunity. The life-time risk of developing HZ was calculated to be 28% for England and Wales [30]. It is more usual in immunocompromised patients and patients over 50 years, and is unusual in children [31].

Varicella is characterised by fever and a generalised, pruritic, vesicular rash, typically consisting of 200 to 500 lesions in varying stages of development and resolution. The rash progresses rapidly from macules to papules to vesicular lesions before crusting. Successive crops (usually two to four) appear over several days. The rash tends to have central distribution, with the highest concentration of lesions on the trunk [31]. Lesions can also occur on mucous membranes and cornea [5].

Humans are the only VZV reservoir which can be transmitted person-to-person by direct contact with respiratory secretions or inhalation of vesicle fluid (airborne spread) [31].

The period of communicability goes from one to two days before the onset of the rash to when the lesions are crusted over, usually four to five days after the appearance of the rash. The incubation period goes from 10 to 21 days, commonly 14 to 16 days [31].

Although most people with varicella make full recoveries, complications can occur, especially in older age groups, pregnant women (including congenital varicella syndrome and neonatal varicella) and immunocompromised patients. Varicella is responsible for a substantial burden of hospitalisations, with variations among countries [31].

The diagnosis of varicella is primarily clinical. Confirmation through laboratory tests is sought mostly in complicated cases, in populations at high risk of serious complications or for epidemiological purposes [31].

4 Burden of varicella in Europe

4.1 Short description of varicella and herpes zoster surveillance systems in the European Union

Information on varicella and HZ surveillance is available via surveys performed by European networks such as the former EUVAC.NET [32,33] or VENICE [34]. In the EUVAC.NET survey [35], 79% (23/29) of the EU/EEA countries had some kind of surveillance system in place for varicella, varying widely among the countries: case-based mandatory reporting at national level (eight countries) or regional level (one country); aggregated data from mandatory reporting at national (seven countries) or regional level (one country); laboratory-based mandatory reporting at national level (two countries) and sentinel surveillance, either alone (six countrywide and one regional system) or as an additional data source (four countries).

Therefore, case definitions, cases collected (all cases vs. cases with complications), data availability (case-based vs. aggregated) and types of cases included in the surveillance (i.e. clinical, laboratory, epidemiologically-linked) vary considerably depending on the country. Very few countries have an extensive set of variables available. Varicella is not included in the EU/EEA list of diseases for surveillance [36], so countries are not bound to a standard case definition.

Of the 17 countries with recommendations on varicella vaccination, ten relied on nationwide mandatory reporting of varicella, three on sentinel surveillance, two countries combined regional mandatory reporting with sentinel surveillance and two countries had no varicella surveillance in place. Five countries have established mechanisms for monitoring varicella vaccination coverage.

With regard to HZ, 11 countries had some form of surveillance in place (IE having a double system): clinician-based sentinel surveillance was conducted in six countries, five on a nationwide basis (BE, FR, DE, IE, NL) and one regionally (UK–England and Wales). Six countries had other forms of surveillance (CZ, ES, IE, MT, SK, SI) and eighteen countries had no HZ surveillance in place.

Conclusions

- The surveillance systems for varicella and HZ in the EU/EEA are highly heterogeneous or completely absent in several countries and most countries have no surveillance system for HZ.
- Even where surveillance systems exist, the degree of underreporting may be considerable, as surveillance is passive and varicella patients do not always see a doctor.
- Existing systems for surveillance of severe cases and complications are limited (in some instances national data sources have been used instead to study these outcomes).
- Vaccine coverage data are missing in several countries which have adopted varicella vaccination recommendations.

4.2 Seroprevalence of varicella antibodies

Serosurveys provide a good estimation of the age at which infection is acquired. However, in most of the studies reviewed, there was no randomly selected representative sample of the population. As an alternative, residual specimens of sera taken for routine diagnostic tests were used to estimate the seroprevalence.

Serological studies across the EU/EEA show rapid acquisition of antibodies to VZV during early life and by 15–19 years most individuals are seropositive [19,37]. Enzyme linked immunosorbent assays (ELISAs) have been used to test for antibodies to VZV in these studies. A multi-country study by Nardone contained a procedure for standardising to common units [19].

However, there are some differences in the average age of infection between the countries, as antibodies following infection are acquired at an earlier age in some countries than in others. Overall, it was observed that seroprevalence was marginally lower among children, adolescents and young adults in southern and eastern European countries [19,38-41] than in northern and western Europe [19,42-47]. Countries such as Belgium or the Netherlands report a higher seroprevalence among children under four years than other parts of the EU/EEA. Early acquisition of varicella has been attributed to the extensive use of pre-school facilities and day-care nurseries, sometimes from as early as three months of age [19,48]. On the other hand, over 5% of individuals aged 20–29 years were seronegative in Italy, Ireland, Spain and England and Wales [19,37,49].

At birth, the majority of neonates are reported to be seropositive for anti-VZV antibodies, probably due to the presence of passively acquired maternal antibodies. In the subsequent months after birth, the percentage decreases drastically to less than 10% between six and nine months and reaches a nadir by around twelve months [42,50-52]. Additional evidence from Leuridan 2011 in Belgium [53] and Waaijenborg 2013 in the Netherlands [54] shows mean duration of protection against varicella for newborns of non-vaccinated mothers to last 2.4 and 3.4 months, respectively.

None of the studies reviewed reported a significant age-specific difference in seroprevalence by sex. A study by van Lier published in 2013 [55] found that geometric mean concentrations (GMC) for VZV antibodies were significantly lower for women than for men aged 20 years and older, however the GMC levels were still well above the cut-off.

4.2.1 Seroprevalence in specific groups

Healthcare workers
Healthcare workers are at higher risk of exposure due to the nature of their work. Furthermore, varicella infection in healthcare workers could result in nosocomial transmission of the infection to susceptible persons in whom varicella could be more severe, such as immunocompromised individuals or pregnant woman.

Seven studies were found that reported the prevalence of anti-VZV antibodies among healthcare workers and medical students. This prevalence was relatively high, ranging from 87.8% to 99.6% [56-62]. Seroprevalence figures for medical students were marginally lower (92.4–98%) [59-61] [62] than for healthcare workers (94.5%– 99.6%) [56-58,61]. One study showed that healthcare workers under 26 years were twice as likely (95% CI: 1.2 to 3.2) to be susceptible to varicella than those over 40 years (12.2% versus 6.6%, respectively) [61].

Pregnant women
In five [63-65] of the seven studies on varicella seroprevalence in pregnant women, less than 5% of pregnant women were seronegative to VZV antibodies. However, a Spanish study [66] found 12% of pregnant women aged 29–35 years to be seronegative and an Italian study found 10.6% of those aged 15-49 years to be seronegative [67].

Non-EU born/immigrants
In a Dutch study [68], seroprevalence for varicella was lower among first generation immigrants (90–92%) than among those born in the Netherlands (97–98%). Additionally, data from van Lier in 2013 [55] found that in children under six years, seroprevalence was lower among first-generation immigrants (53.8%) than among Dutch children (64.0%). A study conducted in the UK [69] found 85% of pregnant Bangladeshi-born women seropositive compared with 93–95% of those born in the UK.

Conclusions

- Overall, VZV circulates widely in all EU/EEA countries and in most countries the acquisition of antibodies to VZV takes place between the ages of two and ten years.
- Antibodies are acquired at an earlier age in some countries than in others.
- Most neonates are seropositive at birth, due to the presence of passively acquired maternal antibodies.

4.3 Incidence of varicella

In most of the studies reviewed, the incidence of varicella had been estimated retrospectively using data from surveillance networks (or hospital-based records in some countries for EUVAC.NET). Only five studies reported incidence based on prospective follow- up of the study population.

It has to be taken into account that surveillance systems for varicella in the EU/EEA are highly heterogeneous or absent in several countries, and underreporting is expected as reporting is mainly passive and many cases do not visit a doctor.

In the absence of vaccination, the annual number of varicella cases in a country is close to a country's birth cohort. The literature review showed that varicella cases primarily occur in the younger age groups. The included studies report that 52–78% of the incident cases occur in children six years or under, and 89–95.9% of the cases occur before adolescence (i.e. under 12 years of age) [37].

Reported, standardised annual incidence per 100 000 population ranged from 300–1 291 in western Europe (FR, NL, DE, UK) [43,52] [70-72], to 164-1240 in southern Europe (IT, ES, PT, SI) [40,70,73-83] and 350 in eastern Europe (PL, RO)[84,85]. Overall, these results indicate that varicella is a common infection in childhood.

The annual incidence of cases among children 1-4 years old was found to vary from 1.580-12.124 cases per 100,000 population and among children 0-4 years old from 4.400-18.600 per 100,000 population [75,76,84,86].

The incidence of varicella per age group was found to vary depending on the country or region within the EU/EEA. Incidence rates in the age group 0–4 years were found to be four to six times those in the age group 5–14 years in in western and northern European countries, compared with two to three times for southern and eastern European countries [86]. This may reflect different contact patterns of children in the various countries.

Data from EUVAC.NET [87] show that in 2010, a total of 592 681 varicella cases were reported from 18 countries that provided epidemiological data based on mandatory notification systems covering the total country population. The highest incidence was reported from Poland, Czech Republic, Estonia and Slovenia (481, 459, 458 and 444 cases per 100 000 inhabitants, respectively). The countries which contributed most cases were Poland (31% of the total), Spain (27%) and Czech Republic (8%).

For the 72% of the cases where age was known, 3% were <1 year old, 41% were 1–4 years of age, 38% were 5– 9 years, 10% were 10–14 years, 3% were 15–19 years and 6% were over 20 years.

4.3.1 Pregnant women

Only two studies from the UK have reported on the incidence of varicella during pregnancy [88,89]. The incidence of varicella requiring hospitalisation in pregnant women was reported to be six cases per 10 000 hospital deliveries in one study (69). In the other study, the overall incidence of varicella in pregnant women was reported to be 0.38 per 1 000 live births [89].

Conclusions

- In the absence of vaccination, the annual number of varicella cases in a country is close to a country's birth cohort.
- Findings confirmed that reported cases of varicella primarily occur in the younger age groups. The studies included have reported that 52–78% of the incident cases occur in children aged six years and under and 89–95.9% of the cases occur before adolescence (i.e. before 12 years of age.)
- The incidence of reported cases of varicella per age group was found to vary depending on the country or region within the EU/EEA.

4.4 Force of varicella infection

A few studies conducted in EU/EEA countries have reported on the age-specific force of varicella infection (rate at which susceptible individuals become infected) [19,90,91].

In general the highest force of infection was amongst 5–9-year-olds in all countries. However, in some countries such as Belgium the highest force of infection was found in the younger age group.

Additionally, a wide variation has been found in the herd immunity thresholds for varicella infection (the proportion of the population that needs to be immunised in order to eliminate endemic transmission of infection and thus eradication of the disease). The thresholds estimated ranged from 70% in Italy to 94% in the Netherlands.

Conclusions

- Varicella infection may be sensitive to differences in mixing patterns, especially in the younger age groups.

4.5 Healthcare utilisation due to varicella disease

The management of varicella cases varies across countries because of differences in EU/EEA healthcare systems and in the way healthcare services are accessed, making it difficult to compare the healthcare use of varicella patients in the EU/EEA.

4.5.1 Hospitalisations due to varicella

Most of the hospitalisation data come from ad-hoc studies and from EUVAC.NET surveillance reports.

Differences in study methods make it difficult to compare the incidence of hospitalisations due to varicella in the EU/EEA. Additionally, data will depend on the age of infection of varicella in each country.

Studies from European countries show that standardised annual incidence of hospitalisations due to varicella ranges from 1.9–5.8 per 100 000 population [89,92-95] (unstandardised incidence 1.3–23.06 per 100 000 population) [52,77,86,91,96-100].

Overall, the incidence of hospitalisations due to varicella decreases with age in all countries. However, it is important to mention here that almost none of the studies in Europe take into account the denominator of varicella cases [81,101], only the total population. As varicella continues to be a childhood disease in the main, the higher number of hospitalisations in children is likely to reflect the higher number of cases in these age groups rather than the severity of the disease.

The highest incidence is found in the youngest age group (0–12 months), with a range from 23–172 hospitalisations per 100 000 population [52,86,91,93,96,98,99,102,103]. According to one study in Spain [99], 58.4% of hospitalisations occur among children < 10 years of age. In the UK, 70% occur in children < 15 years [104]. Studies on the incidence of hospitalisation in adults suggest a higher hospitalisation rate in the age range 25–44 years, compared with other adult age groups [86,91,99,100,102], even though few cases are expected in older age groups

The mean length of hospital stay for all ages was found to vary between three and eight days [52,89,93,99,101,103-112]. In general, the duration was found to be dependent on age (longer for adults than for children) and on the presence and type of complications (up to 12.3 days in children and 9.1 days in adults for varicella-induced pneumonia or bronchitis) [105].

According to the country, the incidence of varicella hospital admissions per 100 000 children in those below 15 years was 23 in France [86,110]. In children younger than 16 years it ranged from 6.8 in the Netherlands [113] to 26 in France [96,103] to 14.1 [103] in children younger than 17 years (Germany).

EUVAC.NET has published reports on hospitalisations due to varicella for the years 2000–2007 [114], 2008–2009 [115] and 2010 [87]. These reports provide an overview for the countries with epidemiological data obtained through mandatory notification systems covering total country populations. Comparison by age group and country is not possible as only the number of cases, and not hospitalisation rates are presented.

In 2010, the last year with data available, data on hospitalisation were provided by 10 countries [87]. There were 1 647 hospitalised cases (0.9% of reported varicella cases in these countries). Most were aged 1–4 years (31%, n=504), followed by those aged 5–9 years (16%, n=279) and those aged 20 years and over (15%, n=242). No population rates are available. The highest hospitalisation rates were seen among those under one year of age (6%, 160/2 709 cases), among those aged 15–19 years (4%, 65/1 743) and those over 20 years (7%, 242/3 325). The findings are similar to those reported in previous years.

4.5.2 Primary care visits due to varicella

Limited studies were found on general practitioner (GP) consultations for varicella in EU/EEU countries. Additionally, health-seeking behaviour and attitudes towards varicella may differ among countries within Europe and this in turn will influence the burden of varicella on primary care, making the studies difficult to compare. Therefore, consultation rates should not be interpreted as varicella incidence rates.

A sentinel surveillance study in Wales, including 30 volunteer general practices with 226 884 registered, reviewed the epidemiology of varicella for the years 1986–2001 [116]. The annual number of varicella consultations for all age groups ranged from 770 to 2 605 cases per year, with the maximum for children under five years. Brisson and Edmunds found that the average GP consultation rate for varicella and zoster between 1991 and 2000 in England and Wales [104] was 522 per 100 000 persons/year, with an age-specific rate of 4 459 for children aged 0–4 years. The same study found changes in the age-specific varicella consultation rates over time: although the consultation rates had remained relatively stable in children under five years between 1991 and 2000, the rate in older children (5–14 years) and adults (older than 15 years) had roughly halved [104].

In the Netherlands, a retrospective cohort study found a total of 254 GP consultations per 100 000 population per year [52]. Here too, the incidence of GP-consultations was highest in childhood, with a small peak in incidence among 25–34-year-olds (contacts with young children who have high infection frequency).

Conclusions

- The comparison of healthcare use in varicella amongst EU/EEA countries is complex because of different healthcare systems, different health-seeking behaviour, and different attitudes towards varicella; comparisons are further complicated by differences in the methods used to estimate hospitalisation rates.
- Additionally, hospitalisations depend on the age of varicella infection among the countries, as the severity of varicella hospitalisations increases with age.
- In Europe, the incidence of hospitalisations due to varicella per 100 000 population was found to decrease with age in all countries. However, the higher number of hospitalisations in younger ages may reflect the higher number of cases in these age groups rather than the severity of the disease.
- The duration of hospital stay was found to be dependent on age (longer for adults than for children) and on the presence and type of complications.

4.6 Complications due to varicella disease

Varicella is usually a mild disease. However, serious complications and death can occur. Overall, 2–6% of varicella cases attending a general practice are estimated to develop complications [37]. Type and severity of complications may vary among populations or age groups. Comparison of specific complication rates is difficult, as the applied definitions vary between studies.

The most frequent complications are skin and soft tissue superinfections, reported in 8–59% of all hospitalised cases [43,74,79,85,89,96-98,100,103,105,106,108,110-112,117-120]. In France, one study reported an incidence of bacterial skin complications of 7.5 per 100 000 children and severe bacterial skin complication of 3.7 per 100 000 children [119].

Neurological complications are the second most frequent, reported in 4-61% of all hospitalised children [74,77,79,85,89,97,98,100,103,108,110-112,117,121-123]. In Germany, the overall incidence of neurological complications in children ≤16 years of age was estimated as 2.4 per 100 000 population [103,124] (corresponding to 4.9 neurological complications per 10 000 varicella cases). In the Italian region of Tuscany, the incidence of central nervous system complications in children 14 years or younger ranged from one to 3.5 per 100 000 depending on the year studied (0.5–1.7 per 1 000 varicella notified cases) [122]. The incidence of meningitis/meningo-encephalitis was reported to be 2.1 per 100 000 population in Slovenia [83], whereas in the Netherlands the incidence of acute cerebellar ataxia is estimated to be 0.25 per 100 000 population [93].

Complications of the respiratory system, especially pulmonary complications have been reported in 3–22% of hospitalised cases [97,103,112]. The main clinical manifestations include pneumonia (due to VZV or other pathogens) and otitis media [77,79,88,100,103,111,118]. In Slovenia, the reported incidence of pneumonia is 0.8 per 100 000 population [83].

Other complications (i.e. gastrointestinal, hepatic and haematological) have been also reported [74,79,103,111,112]. In Tuscany, the incidence of hospitalisations due to complications of the non-central nervous system (respiratory, renal, haematological, osteoarticular and infectious) ranged from 8.3–12.0 per 100 000 children (4.9–5.6 per 1 000 varicella notified cases) [122].

Long-term sequelae have been reported in 0.4–3.1% of patients hospitalised due to varicella infections [103,108,117] and in up to 40% of patients hospitalised from varicella due to severe complications [102]. Possible long-term sequelae have been reported in 8.7% patients hospitalised due to varicella [103]. Most frequent sequelae included severe cutaneous scarring, ataxia/coordination disorders, epilepsy or cerebral nerve paralyses.

Varicella is a serious infection at any stage of pregnancy. Varicella in the first 20 weeks of pregnancy has been associated with an incidence of congenital varicella syndrome (0.91%) [125], at 0–12 weeks gestation with an incidence of 0.4% and at 13–20 weeks gestation with an incidence of 2% [126]. Maternal varicella four days before to two days after delivery can cause generalised neonatal varicella, which leads to death in about 20% of untreated cases [125]. Moreover, in pregnant women with varicella, there were instances of varicella pneumonia in 10–20% of the cases [127].

The severity of varicella varies with the age of the individual. Following a high risk of complications during pregnancy and around birth (congenital varicella syndrome and neonatal varicella), the risk of complication is low during the first three months of life, probably due to the presence of maternal antibodies [128]. Subsequently, the

risk of severe varicella is higher in infants and adults than in children [86]. Data on complications in Europe mainly relates to the incidence of complications and data on hospitalisation rates among varicella cases is scarce.

In Germany, a country-wide sentinel surveillance system initiated after implementing routine varicella vaccination [118] reported that most of the complications occurred in 0–4 (59%) and 5–9 (31%) year-olds, however, as stated above, these data may just reflect the fact that these are the age groups where most cases occur.

In one study the incidence of complications in individuals under 16 years was reported as 8.5 per 100 000 population [120].

The type of complications are also reported to vary with age: the most common complications for children under 12 years are bacterial superinfections, otitis media, pneumonia and bronchitis. For the older age group, bacterial superinfections and lower respiratory tract infections are the most common [43]. It has also been observed that neurological complications usually occur in older age groups, whereas severe bacterial superinfections occur in younger age groups [103].

Being immunocompromised is a risk factor for severe varicella [129]. However, most complications and hospitalisations for varicella were found to occur among children who were immunologically healthy with no underlying medical conditions [99,103,108,118,121]. Among 3 632 primary varicella-related hospital discharges in Spain (all ages), 8% had an underlying condition recorded [99]. In the Netherlands, a study on hospital admissions due to varicella from 2003 to 2006 reported that 39% of hospitalised cases had an underlying condition [113]. In a study of 1 575 paediatric hospitalised varicella cases in France, 8.3% of cases had corticosteroid therapy, 1.3% had received immunosuppressant chemotherapy and 4.1% had an underlying disease [108]. A prospective German study, including 918 varicella hospitalised cases where 7% were immunocompromised, showed that varicella complications, including coagulation disorders, lower respiratory tract complications and systemic bacterial infections, were significantly more frequent (p<0.001) in immunocompromised than in immunocompetent children. In contrast, the most common complications, such as neurological (p< 0.054) and skin infection complications (p<0.012) were significantly more frequent among immunocompetent children [103].

EUVAC.NET reports incidence data on complications in hospitalised cases due to varicella for five countries in 2008, 2009 [115] and 2010 [87] (GR, HU, NO, SK and SL for 2008–2009; EE, GR, HU, SK and SL for 2010). A total of 90 cases with complications were reported in 2008, 75 in 2009 and 153 in 2010.

These results have to be interpreted carefully, as it is possible that the assumption of causality between disease and potential complications could have resulted in misclassifications. Additionally, comparison of specific complication rates is not easy as studies adopted different classification methods.

Conclusions

- Though most persons with varicella make full recoveries, 2–6% of varicella cases attending a general practice are estimated to develop complications.
- The most frequent complications are skin and soft tissue superinfections, followed by neurological and pulmonary complications.
- Long-term sequelae have been reported in 0.4 to 3.1% of patients hospitalised due to varicella infections.
- Varicella is a serious infection at any stage of pregnancy both for the mother (higher morbidity/mortality than in non-pregnant adults) and for the child (can lead to congenital varicella syndrome or neonatal varicella).
- The risk of severe morbidity is higher in immunocompromised children, however most complications and hospitalisations involving varicella occurred in those who were immunologically healthy with no underlying medical conditions.
- The risk of severe varicella and complications is higher in infants and adults than in children.
- Type of complications may vary among populations or age groups. Neurological complications usually occur at an older age.
- Comparison of specific complication rates is difficult, as almost every study adopted different classification methods.

4.7 Varicella-related mortality

Case fatality ratios in studies from EU/EEA countries vary from 0.01% to 5.4% among hospitalised cases of varicella [77,95,98-100,102,103,107,109,112,116,121,124,128,130,131]. In a study in England and Wales from 1993 to 2000 an average of 25 people a year died of varicella (0.05 deaths per 100 000 population-year); the age-specific case-fatality rate was low in children (less than 1 per 100 000 cases) but increased dramatically in adults (nine deaths per 100 000 cases in 15–44-year-olds, 73 deaths per 100 000 in 45–64-year-olds and 689 deaths per 100 000 cases in those over 65 years) [104]. Other studies found that subjects over 15 years are at 16 to 30-fold greater risk of dying than children aged 1–4 years. However, the mortality rate among adults is not uniformly distributed, as most deaths occur among the elderly [86,89,104]. A potential misclassification of varicella as a

cause of death in the elderly has to be taken into account. One study in the UK has assessed that 20% of varicella death certificates were misclassified as HZ [132].

In general, most of those who died of varicella were reported to have been previously healthy individuals. Population-based studies found that underlying conditions were present in approximately 20–30% of the deaths (generally immunosuppressive disorders such as acute lymphoblastic leukaemia) [86,100,101,103,107,128,133].

The common causes of death reported were septicaemia [101,103,107,117,121,128], pneumonia (due to VZV or other pathogens) [100,103,117,128], acute respiratory distress syndrome [103,128], myocarditis [117], endotoxic shock [107,117] or encephalitis [100,101,107]. Two studies reported fatalities among infants born with congenital varicella syndrome [103,128].

Accuracy of data regarding mortality can be affected by misclassification of the cause of death.

Conclusions

- Case fatality rates were found to vary from 0.01% to 5.4% among hospitalised cases of varicella.
- Persons over 15 years of age have a greater risk of dying than children aged 1–4 years.
- Most of those who died of varicella were reported to have been previously healthy individuals.

5 Varicella vaccines

5.1 Background

In 1974, Takahashi and colleagues at the University of Osaka developed an attenuated strain of varicella virus suitable for vaccine production. This strain, called the OKA-strain, is used in production of varicella vaccines licensed in Japan, Europe, USA, and the vast majority of countries worldwide. One of the first clinical trials using an OKA strain containing vaccine included 70 healthy children in Japan exposed to household contacts with varicella. The vaccine offered definite protection when given within three days of exposure.

Several dose-ranging studies and double blind protection trials followed. Since immunocompromised children are at high risk of complications or even death due to varicella, clinical trials of varicella vaccination of children with acute leukaemia or other malignant diseases were started in the late 1970s. The results showed that immunosuppressed subjects could be safely vaccinated if chemotherapy was suspended around the time of vaccination, provided that they had acceptable lymphocyte counts or were in remission. To date vaccination of children and adults in regular or close contact with high-risk individuals is widely recommended in Europe.

Several monovalent and combined live attenuated varicella vaccines authorised in the EU/EEA were derived from the parenteral OKA strain by further passaging in cell culture. These vaccines are distinct in their virus passage history and vaccine composition. The currently licensed monovalent vaccines Varivax (OKA/Merck) and Varilrix (OKA/RIT) contain no less than 1 350 and 2 000 plaque-forming units (PFU) respectively per dose at expiry. In order to support the implementation of routine varicella vaccination and to accommodate childhood vaccination programmes worldwide, two combined MMRV live attenuated vaccines, ProQuad (OKA/Merck) and Priorix Tetra (OKA/RIT), were developed. However, due to immunological interference of the different virus vaccine components observed in clinical trials, the composition of the combined MMRV vaccines had to be adapted. In the final approved formulation of Priorix Tetra the amount of mumps virus was increased while the varicella virus concentration remained the same as in Varilrix. In contrast, the varicella virus concentration was increased from at least 1 350 PFU per dose in Varivax to at least 9 900 PFU per dose in ProQuad. The three other vaccine components in ProQuad correspond to the approved virus concentration in the respective MMR (measles, mumps and rubella) vaccine.

Results of vaccine efficacy, immunogenicity and safety obtained from controlled, randomised clinical studies of healthy children are summarised in Sections 5.2 and 5.3. For vaccine effectiveness data reported after implementation of routine immunisation programmes see Chapter 6.

5.2 Efficacy and immunogenicity

Protective vaccine efficacy against varicella disease was demonstrated in various randomised, controlled clinical trials in healthy children [134-137] [129,138-141]. In early clinical trials employing varicella vaccines with various live virus concentrations, protective vaccine efficacy in healthy seronegative children varied between 72–100% following administration of a single dose [138,139]. Further studies compared the protective efficacy following a one-dose with a two-dose vaccination regimen for different varicella-containing vaccines, both OKA/Merck and Oka/RIT [134-136]. In a study employing the OKA/Merck strain, the estimated vaccine efficacy against all severities of varicella disease for a 10-year observation period was 94% for one dose and 98% for two doses of a monovalent vaccine. Both the one- and two-dose regimens were 100% efficacious against severe varicella [134]. Vaccine efficacy for the OKA/RIT strain was assessed over a follow-up period of 35 months in an actively controlled, randomised clinical trial of children in their second year of life. Vaccine efficacy against confirmed varicella of any severity was reported to be 65.4 % after one dose of an OKA/RIT-containing vaccine and 94.9% after two doses. Vaccine efficacy against moderate or severe confirmed varicella was found to be 90.7% after one dose and 99.5% after two doses [135,142]. In these clinical efficacy trials the relationship between primary antibody responses and the risk of post-vaccination BV was assessed using statistical modelling, since no commonly accepted surrogate marker for protection has been established. A continuous relationship between antibody titre and the probability of experiencing a BV event was demonstrated although no antibody titre correlated absolutely with protection. Using a glycoprotein based enzyme linked immunosorbent assay (gpELISA), a post-vaccination antibody titre of ≥ 5 gpELISA units/ml was defined as an approximate correlate for protection for the OKA/Merck vaccine, whereas a titre of ≥ 50mIU/ml was set as the threshold for a commercially available whole-cell ELISA assay to calculate response rates [143] (unpublished data). In addition, VZV-specific antibody responses were measured by immunofluorescence assays (IFA). A serum dilution of 1:4 or higher was considered positive. Immunofluorescence antibody titres correlate with neutralising antibody titres and it was found that a titre of more than 1:4 at the time of exposure correlates with protection against chickenpox after vaccination and natural infection [144].

Immunogenicity of varicella vaccines was evaluated in children, adolescents and subjects at risk in numerous clinical trials following different vaccination schedules and administration methods and using serological assays

with different levels of sensitivity. After primary vaccination of seronegative healthy children in their second year of life with a single dose of monovalent varicella or MMRV vaccine, seroconversion rates against varicella of 85–100% were reported [140,145-150]. The response rates were comparable, irrespective of whether a single dose of monovalent varicella vaccine was given concomitantly with a single dose of MMR vaccine or subsequently (six weeks apart), or whether a single dose of combined MMRV vaccine was administered [140,145,148,149,151-153]. Moreover, the route of administration (i.e. either subcutaneous or intramuscular injection) had no impact on the immune response [154,155]. Regarding vaccine brand, a study comparing a single dose of Varivax with a single dose of Varilrix found seroconversion rates were slightly higher in recipients of Varivax [156]. For tetravalent vaccines, a recent study comparing both tetravalent vaccines (when coadministered with other vaccines) found that Piorix Tetra was not inferior to Pro-Quad for the responses to the MMR competent, but this was not demonstrated for the varicella component [157].

Comparison of immune responses following a one or a two-dose vaccine regimen revealed that a significant increase in antibody levels (approx. 10–20-fold) and higher seroconversion rates were elicited among the two-dose vaccine recipients than in subjects receiving a single dose. This booster effect was achieved irrespective of the time interval between administration of the first and second dose. Comparable antibody levels and response rates were obtained regardless of whether the second vaccine dose was given 6–12 weeks or 3–6 years after the first dose [148,152,158-160].

Data comparing the immune responses of children and adults/adolescents indicate that the vaccine is less immunogenic in adults and adolescents. In early clinical trials of the OKA/Merck monovalent varicella vaccine, seroconversion rates of over 95% were reported among children and adolescents up to 12 years after a single dose, while adolescents aged 13–17 years only had a seroconversion rate of 79% [146]. Due to the application of a low cut-off level in the serological assay these data most likely overestimate the protective antibody responses. In other studies it was found that antibody response against varicella was less vigorous in seronegative adult subjects than in children and that a second dose significantly increased the response rates [161,162].

In an era of external exposure to varicella, antibody persistence in the US was demonstrated for a period of up to nine years post vaccination using a one and two-dose vaccination regimen [134]. An increase in antibody levels was observed in the first years following vaccination, particularly in one-dose vaccine recipients, indicating a boost in antibody levels following exposure to circulating wild-type virus. Subjects who received two vaccine doses within three months generally had higher antibody concentrations during the first three years compared to single dose recipients. However, there were no significant differences in antibody levels between the one and two-dose regimen by the end of the nine-year time period.

A systematic review of the evidence on effectiveness and duration of protection of varicella vaccines has been recently published by the WHO Strategic Advisory Group of Experts on Immunisation (SAGE) Working Group on Varicella and Herpes Zoster Vaccines in 2014 [163].

Two studies comparing immunogenicity between OKA/Merck and OKA/RIT monovalent or tetravalent vaccines have been conducted, showing lower post vaccination titres in OKA/RIT-derived vaccines [156,157].

Conclusions

- Efficacy and immunogenicity results obtained in controlled clinical studies confirm that monovalent and combined varicella vaccines are highly immunogenic and efficacious in preventing varicella disease. Efficacy is higher against severe varicella than against less severe varicella.
- A two-dose vaccination regimen results in higher seroconversion rates and vaccine efficacy than a single-dose administration.
- A second dose given six to twelve weeks after the first dose elicits comparable antibody responses to the administration of a second dose at 3–6 years.
- There is a continuous relationship between antibody titre and the probability of BV, even though a protective antibody titre has not been defined.
- Gaps and uncertainties include the duration of immunity, the risk of complications in BV cases many years after vaccination (which could depend on the number of doses), the need and optimal timing for a second dose, and long-term effects of varicella vaccination further than 14 years (e.g. maternal antibody levels in newborns from varicella-vaccinated mothers)

5.3 Safety

Varicella vaccines are live attenuated and are in principle contraindicated in immunocompromised individuals in order to avoid severe disseminated varicella infection. For further reference see Rubin 2014 [164].

For varicella and MMRV vaccines a substantial safety database is available from clinical trials and through worldwide post-marketing experience, with millions of doses distributed.

In clinical trials of children aged 12 months or older, monovalent and combined varicella vaccines were monitored for up to 42 days after each vaccination. The vaccines were generally well tolerated following one- or two-dose vaccine regimens. The most frequently reported adverse events were injection site reactions such as pain, redness or varicella-like rash, which were mostly mild and transient. The most commonly reported vaccine-related systemic reaction was fever.

No serious adverse events were observed for monovalent vaccines and very few were reported for MMRV vaccines. Serious adverse effects following vaccination with MMRV included febrile convulsion, urticarial allergic reaction, fever, cough and bronchiolitis [153]. All subjects recovered without sequelae.

For the combined MMRV vaccines, the incidence of adverse reactions did not differ significantly from the concomitant use of MMR and varicella vaccines. As expected, injection site reactions were reported at a statistically lower rate in individuals who received the combined MMRV vaccine than for concomitant use of varicella and MMR vaccine.

Post-marketing experience with varicella and MMRV vaccines generally confirmed the safety profile established in clinical trials. In all age groups a low number of rare, serious adverse reactions were experienced [165]. Chaves et al. [166] reviewed the US Vaccine Adverse Event Reporting System data from 1995 to 2005 (where the Oka/Merck vaccine was used) and found 2.6 serious adverse events per 100 000 doses distributed. In children, a higher proportion of reports related to varicella vaccine administered in combination with other vaccines were classified as serious than the proportion of reports related to varicella vaccine administered alone [166].The most frequently reported serious adverse events that were most likely related to varicella vaccines were severe disseminated varicella, pyrexia, convulsions and HZ.

It was found that the vaccine-strain may cause severe or even fatal varicella disease in immunocompromised subjects [Maves et al. 2013]. However, the risk of varicella vaccine virus being transmitted from healthy persons to susceptible contacts is very low. With more than 55 million doses of VARIVAX distributed, transmission from immunocompetent persons after vaccination has been documented by PCR analysis in only five persons, resulting in six secondary infections, all of them mild [167].

As regards reported HZ cases, laboratory tests demonstrated that they might be associated with vaccine or wild-type varicella virus [168,169], indicating reactivation of the vaccine virus strain and BV events. Some cases of HZ were associated with meningitis and encephalitis, but only in one case of a mild form of encephalitis was the OKA vaccine strain detected by PCR [141, 145]. Surveillance data on vaccinated individuals suggest a decrease in the frequency of HZ in this population [170-172].

In addition to the neurological complications associated with HZ, isolated cases of encephalitis, meningitis and cerebellar ataxia were reported, which are known to also occur following wild-type varicella infection. None of the clinical specimens tested by PCR were found to be positive for the OKA vaccine strain [165].

Fever (transient without long-term sequelae) and a measles-like rash were reported at a significantly greater rate in MMRV [153] than in MMR+V. However, the most salient safety finding after widespread use of MMRV in routine practice was an increased risk of febrile seizures. Analyses of post-marketing studies in children receiving their first dose of MMRV vaccine have shown that febrile seizures occurred more frequently five to twelve days after vaccination in the order of one additional febrile seizure for every 2 600 to 2 700 vaccinations compared with separate MMR and V injections [173] [174] [175]. Among 12–23-month-old children the risk of febrile seizure occurring was determined to be twice as high in MMRV vaccine recipients during the seven to ten days after the first dose. This means that one additional case of febrile seizures was observed for every 2 300 MMRV doses given [174].

Similar observations were reported for a matched cohort study performed in Germany [175] and published by Schink in 2014 . These increases are similar for Proquad [173] and Priorix-Tetra [176], suggesting a class effect for these quadrivalent vaccines. No increased risk was observed following a second dose. As a result of these findings the national recommendations for use of MMRV vaccines were revised in the USA, Italy, Greece and Germany (in Germany, a separate vaccination for the first injections is now recommended [177,178]). Klein et al. (2012) [179] used Vaccine Safety Datalink data to examine the risk of febrile seizures in children four to six years of age following MMR+V and MMRV. They found no evidence of an increased risk during the six weeks after vaccination.

Conclusions

- The most common adverse reactions following varicella vaccine are local reactions, such as pain and erythema.
- Monovalent and combined varicella vaccines are generally well tolerated, with the exception of an increased risk of one febrile seizure among every 2 300 children vaccinated with a first dose of MMRV vaccine given at age 12–23 months.

5.4 Post-marketing studies on varicella vaccine effectiveness

This section presents information on BV and varicella outbreaks in vaccinated populations. For effectiveness studies conducted in countries with universal varicella vaccination, see Chapter 6.

5.4.1 Breakthrough varicella

A BV infection is defined as a case of wild-type varicella that occurs in a vaccinated person more than 42 days after varicella vaccination, following exposure to wild-type virus.

BV is usually mild, with less than 50 skin vesicles compared to 200-400 lesions in immunologically naive patients [180-182].

Several observational studies have reported frequency of BV in vaccinated individuals and results vary significantly between studies and years of observation [183-189]. This may be related to differences in the studies (e.g. study conducted in a country with universal vaccination coverage, vaccination coverage reached, type or dose of vaccine administered, study population (e.g. age), or time since vaccination). Seward et al. estimated in a review that a single dose of OKA/Merck varicella vaccination in children is 85% effective in preventing all varicella (median; range 44–100% in post-licensure studies) [190], therefore approximately 15% of vaccinated individuals may develop BV if exposed to VZV. Other surveillance and case control studies in the USA have suggested an effectiveness of one dose of varicella vaccine of 71 to 87% [191-193].

BV is caused by primary (failure to seroconvert or to mount a protective immune response despite seroconversion) or secondary (waning immunity) vaccine failure.

In a ten-year follow-up study in the USA, the cumulative 10-year rate for contracting varicella more than 42 days post vaccination in children who received two doses was 3.3-fold lower than the rate in children who received one dose (2.2% vs. 7.3%, p < 0.001) [134]. Moreover, in a study in Germany [194], the risk of BV was higher for one dose of Varilrix (RR = 2.8, 95% CI 1.0–7.8, p = 0.05) or Priorix-Tetra (RR = 2.4, 95% CI 0.7–8.3, p = 0.18) than with one dose of Varivax, but lower for two doses of Priorix-Tetra (RR = 0.5, 95% CI 0.1–2.7, p = 0.41). No significant differences in BV rates was found between subjects who had received MMR+V concomitantly or after a six-week interval [140].

Younger age at vaccination (≤14-18 months) may be a risk factor for vaccine failure [195], but the evidence was not consistent and several articles found no association between BV and age at vaccination [181,194,196-202].

Increasing time passed since immunisation may be a risk factor for vaccine failure. In general, most studies showed that mild BV rates do not seem to increase over time since immunisation (<10 years) in children or adults at risk of exposure [140,181,182,198,199,202-204]. However a few studies [200,202,205-207] reported significantly higher risk ratios for children vaccinated over five years ago than for children immunised more recently. There are inconclusive data on the increasing severity of BV with the passing of time since immunisation [134,207,208].

Another recent study by Baxter et al. in 2013 [172] showed that at the end of the 14-year study period (including children vaccinated mainly with one dose and for the last three years with two doses) varicella vaccine effectiveness of OKA/Merck vaccine was 90%, with no indication of it waning over time. Most cases of varicella were mild and occurred early after vaccination. However, this study did not account for changing epidemiology and risk of exposure following the two-dose schedule introduced only three years before the study was conducted.

No conclusive evidence is available for the different risk factors of vaccine failure, apart from receiving varicella vaccine within 28 days of MMR vaccine. Nevertheless, a recent review published by Bonanni et al. in 2013 reviewing primary and secondary failure after varicella vaccination [209] showed that most cases of BV could be accounted for by primary vaccine failure. A small study by Redondo-Granado in 2013 [210] reviewing 10 years of BV in children vaccinated with one dose showed that half of the BV cases happened within two years of vaccination. Additionally, no consistent trend between BV rate and time since vaccination was found, pointing to a limited evidence of secondary varicella failure.

Conclusions

- BV is usually mild.
- No conclusive evidence is available for the different risk factors of vaccine failure; however, effectiveness of one dose has shown vaccine effectiveness around 80%, pointing to some primary vaccine failure.
- Recent studies show no consistent/limited evidence of secondary varicella failure.

5.4.2 Varicella outbreaks in vaccinated populations

Annual outbreaks of varicella are common in non-vaccinated populations. Varicella is a highly transmissible disease with secondary attack rates of 60–100% in susceptible contacts [194]. The description of outbreaks in vaccinated populations provides an opportunity to study vaccine effectiveness, risk factors for BV and vaccination coverage, even though different vaccine coverage rates in the different countries make it difficult to draw relevant conclusions regarding the control of outbreaks with the varicella vaccine.

Most of the outbreaks in vaccinated populations described to date in the USA [199,200,205,211-213], Germany [194], Spain [202], Israel [214] and Uruguay [215] have been studied and provide useful information for understanding varicella in vaccinated populations. Outbreak situations offer an opportunity to evaluate the effect of immunisation in the field where it is most useful and where there is a high risk of infection.

The vaccination coverage in the populations of these countries is quite different, ranging from outbreaks in communities with low vaccination coverage (Israel) to communities with high vaccination coverage (Uruguay). In one of the countries (Germany) where different varicella vaccines are used, vaccine effectiveness could be calculated for vaccines brand; vaccine effectiveness for one dose of Varilrix and Priorix Tetra was found to be lower than for one dose of Varivax [194].

The trends and characteristics of varicella outbreaks in active surveillance sites have been analysed in the USA by Civen et al. and Kattan et al. The study by Civen et al. [212] showed that during a 10-year period (1995–2005), in a population vaccinated with a one-dose schedule, outbreaks significantly decreased in number (from 236 to 46, $p < .001$), in size (from a median 15 cases to nine cases/outbreak, $p < .001$) and in duration (from 44.5 days to 30 days, $p < .001$). The median age of case patients with outbreak-related varicella increased from six to nine years ($p < .001$). The change to a two-dose vaccination had a further impact on the characteristics of varicella outbreaks. Kattan et al.[216] showed that in an active surveillance site during the period 2005–2008, the number and size of school outbreaks of varicella decreased dramatically, with 42 outbreaks during the 2005–2006 school year (mean size, 14; range, 5–62) and only two outbreaks during the 2008–2009 school year (mean size 5; range, 3–6).

Conclusions

- It has been reported that varicella vaccination decreases the number, size and duration of varicella outbreaks and that such decreases are even greater with a two-dose schedule.
- One-dose varicella vaccination strategies have been linked to an increase in the median age of patients during outbreaks (from six to nine years); there was no data available for two-dose schedule strategies.

5.5 Varicella vaccination recommendations in the EU/EEA

WHO advocates routine childhood immunisation against varicella in countries where the disease is a relatively important public health and socioeconomic problem, where the vaccine is affordable and where high (≥ 80%) and sustained vaccine coverage can be achieved [217]. The latter is important as childhood immunisation with low coverage could theoretically shift the epidemiology of the disease and increase the number of severe cases in older children and adults for whom the disease is more severe. Additionally, WHO advocates recommendation of the vaccine in any country to individual adolescents and adults without a history of varicella, in particular to those at increased risk of contracting or spreading the infection. This entails no risk of an epidemiological shift, as childhood exposure to VZV remains unaffected.

In the European Union there are centrally authorised vaccines (e.g. ProQuad [218]) and vaccines which are authorised nationally (Priorix Tetra, Varilrix, Varivax and associated brand names [219]).

Monovalent vaccines are available in 28 countries and combined vaccines (MMRV) in 16 countries (AT, BE, CY, CZ, EE, EL, DE, HU, IT, LV, LU, MT, NL, PL, SK, SI) [220] [updated by public consultation].

In October 2012, there were various types of recommendation regarding varicella vaccination in 22 out of 29 EU/EEA countries [220]. In seven countries there is no specific recommendation for varicella vaccination in the national immunisation plans (BG, CZ, HU, PT, RO, SK, SE).

In six countries (AT, CY, DE, EL, LV, LU) varicella vaccination is universally recommended for children at national level and in two countries (ES, IT) at regional level (see Figure 1, updated from VENICE survey and by personal communication). The year of introduction, number of doses and age of varicella vaccination are summarised in Table 1. In AT and CY vaccination is recommended but not funded by the national health system. Additionally, in the CZ and FI universal vaccination is recommended but not included in the national immunisation programmes.

Sixteen countries (including the two with regional universal recommendation) recommended nationwide vaccination for susceptible teenagers and/or risk groups only.

As regards occupational risk groups, thirteen countries recommended vaccination for susceptible healthcare workers (AT, DE, ES, FR, IE, NL, LU, UK, SI, LT, MT, NO, FI), two countries for susceptible pedagogical staff (AT, FR) and four for susceptible day-care personnel (AT, DE, FR, FI) [220].

Figure 1. Varicella vaccination recommendations in EU/EEA countries, 2012

Data source: From VENICE report 2010, updated by public consultation 2014.
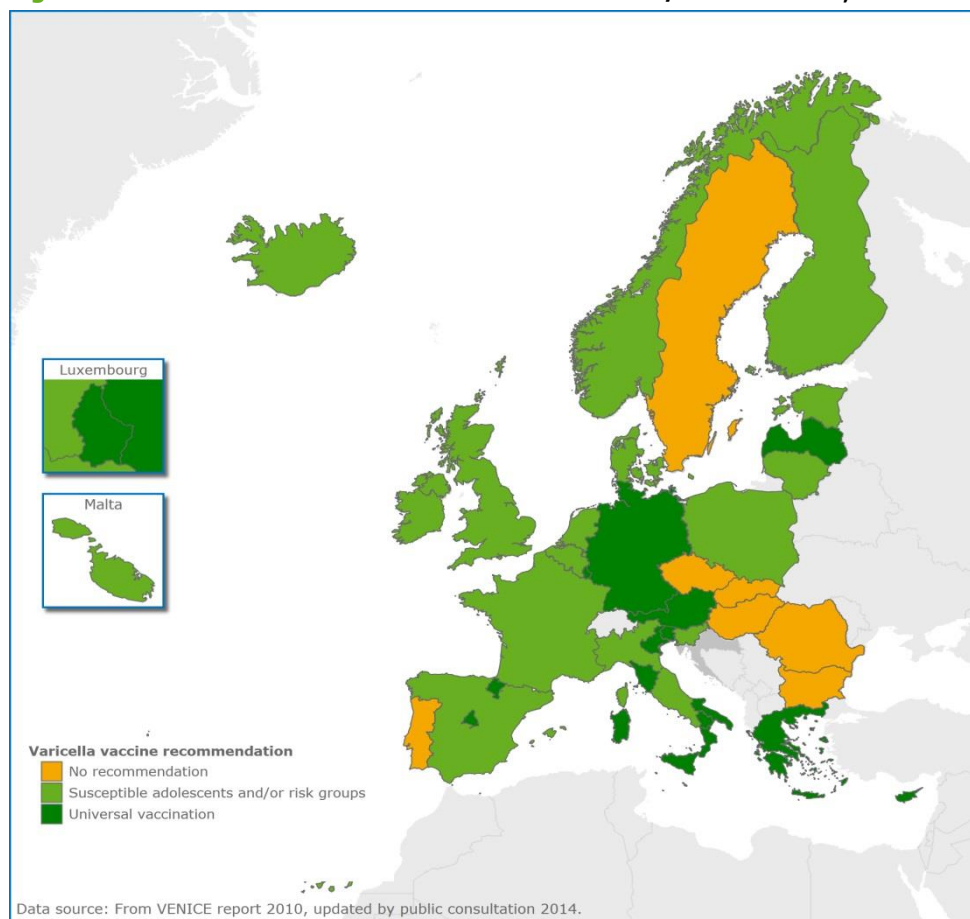
Table 1. Year of introduction, number of doses and age of varicella vaccination in EU and EEA countries with childhood universal vaccination, 2014

	Year of introduction	First dose	Second dose
Germany	2004[1]	11–14m	15–23m
Latvia	2008	12–15m	-
Greece	2006[2]	12–15m	4–6y
Cyprus	2010	13–18m	4–6y
Luxemburg	2009	12m	15–23m
Austria[3]	-	-	-
Italy			
Sicily	2003	2y	-
Veneto	2005	15m	3y
Puglia	2006	13 m	5–6y
Toscana	2008	13–15m	5–6y
Basilicata	2010	13m	6y
Calabria	2010	13–15m	5–6y
Sardinia	2011	13m	6y
Friuli-Venezia-Giulia	2013	13m	6y

	Year of introduction	First dose	Second dose
Spain			
Madrid[4]	2006	15m	-
Navarre	2007	15m	3y
Ceuta	2009	18m	24m
Melilla	2009	15m	24m

[1] *Universal vaccination of infants with one dose was recommended in Germany in 2004, and universal vaccination with a second dose in 2009.*

[2] *Universal vaccination of infants with one dose introduced in Greece in 2006 universal vaccination with a second dose in 2009. [public consultation]*

[3] *Information not available for Austria*

[4] *Programme withdrawn in November 2013*

Conclusions

- Varicella vaccine recommendations in the EU/EEA are heterogeneous: only six countries universally recommend varicella vaccination for children at national level and two countries at regional level.
- Sixteen countries recommend nationwide vaccination for susceptible teenagers and/or risk groups only.

6 Public health impact of varicella vaccination

6.1 EU experience with varicella vaccination

Germany

Germany is the country with the most experience of varicella vaccination in Europe.

Germany introduced universal varicella vaccination for children over 11 months of age in 2004 (one dose) and recommended a second dose in 2009, preferably given between 15–23 months and at least 4–6 weeks after the first dose [221]. Additionally, two doses were recommended for unvaccinated adolescents aged 9–17 years with no previous history of varicella [221]. Until 2007, regional differences in payment and reimbursement of varicella vaccination had an impact on vaccine uptake. Moreover, in Germany all licensed and available vaccines may be used, if complying with the product information. However, the product information was different regarding the schedules for monovalent and tetravalent vaccines until 2009. Therefore, between 2004 and 2009 varicella vaccination in Germany varied by region and schedule.

Varicella-zoster surveillance was mainly carried out by sentinel physicians (ongoing since 2005) [118,183,222], by outbreak investigation (2008/09) [194] and by surveillance of hospitalisations [188].

In countrywide active sentinel-surveillance (Active German Varicella sentinel – AGV), approximately 1 200 primary physicians provided information on aggregated numbers of varicella cases by age or zero-reports, as well as doses of varicella vaccine administered by month (from April 2005 to March 2011) [194]. Additionally, they sent case-in based questionnaires on varicella complications, varicella in vaccinated persons and cases of HZ. Regional, population-based surveillance has been going on in the Munich area, involving two-thirds (88–98 practices) of all local paediatricians and collecting similar data on varicella and herpes zoster cases in children under 17 years since October 2006 (as reported in Streng et al. [223] and in a poster at the ESPID Conference 2013) . Additionally, data on complications associated with varicella-zoster infections were collected from paediatric hospitals in Bavaria [222].

Varicella vaccination coverage was estimated using physicians' billing data on patients vaccinated against varicella, which have been available on a quarterly basis from up to 17 regional Associations of Statutory Health Insurance Physicians since 2004, covering about 86% of the German population. Regional coverage in the Munich area was determined by annual representative parent surveys [224] [223].

Vaccine effectiveness was assessed for outbreaks in day-care settings [194] as well as in a time series analysis using sentinel and coverage data [225], and a recent age and practice-matched case-control study from Liese (2013) [226].

Between April 2005 and March 2009, countrywide sentinel surveillance showed a 55% reduction in varicella cases per reporting physician for all ages; 63% in the age group 0–4 years and 38% in 5–9-year-olds [183]. The decreasing trend has not yet come to an end: by 2012, the case reduction was 84%, as reported in an article by Siedler in 2013 [227]. Meanwhile, in the AGV-sentinel varicella complications decreased by 81% [118].

Regional surveillance in Bavaria yielded similar results: from October 2006 to September 2011, incidence estimates of varicella cases in outpatient children from the Munich area decreased by over 77% (from 78.1 to 19.2 per 1 000 children), even with still suboptimal vaccination coverage [223].

Between 2005 and 2009, the incidence of varicella hospitalisations in children under 17 years in the Munich area decreased by 43% (from 7.6 to 4.3 per 100 000 children), with the strongest reduction (by 77%) observed in children under one year of age, indicating the effect of herd immunity [223]. Based on data from all paediatric hospitals in Bavaria, annual incidence of varicella-associated hospitalisations was estimated to be 13.3 per 100 000 children in 2005 and decreased to 6.7 in 2009 (by 50%) [222] (Streng et al., poster at ESPID Conference 2011).

With regard to HZ, a steady number of HZ cases per reporting sentinel physician was observed during the period of the AGV sentinel surveillance [183]. However, age stratified analysis of paediatric cases showed a decrease of HZ in children 0–4 and 5–9 years and an increase in adolescents 10–14 years. The trends in 0–4 and 10–14 years were confirmed by billing data and national statistics on hospital admissions (unpublished data and Siedler et al., poster at ESPID Conference 2011). Sentinel data has so far not shown any clear trend relating to HZ in adults, but analyses are continuing, also using data from other sources.

As in the nationwide sentinel surveillance, an initial decrease of HZ cases aged 0–9 years was also observed in Munich, but this trend did not continue [Streng et al., poster at ESPID Conference 2013].

During the AGV sentinel surveillance observation period, the number of administered vaccine doses increased overall, but the trend varied by first and second doses, physician's speciality and region [183]. Coverage as estimated by billing data increased over time, indicating a growing acceptance of varicella vaccination in parents and doctors [222,224,228] [223]. Coverage differed by age and region [194,228]. In the first years of the vaccination programme, both sentinel and billing data showed that vaccine uptake and the level of vaccination coverage in the earliest age cohort eligible for the recommended varicella vaccination were significantly affected by the delay in introducing reimbursement [183,228]. According to billing data, coverage was estimated to be about 78% at 24 months in 2008 [225]. For the birth cohort 2009, vaccination coverage was 87% for the first dose at 24 months (64% for the second dose) according to Siedler 2013 [227]. In Munich, first-dose vaccination coverage in children up to three years of age stagnated after initially increasing to 51–53% during the period 2007–2009. With reimbursement of the combined MMR-varicella vaccine in 2009, first-dose vaccination coverage increased (66–68% in 2010-2011) and second-dose vaccination coverage reached 59% in 2011 [189]. Recent data published by Streng et al. [229] showed that separate first-dose vaccination for MMR and varicella, implemented in 2011 due to a slightly increased risk of febrile seizures associated with combined MMR-varicella vaccine, resulted in a 12% decrease in varicella vaccinations in Munich and a (non-significant) 4% decrease in a second regional surveillance region.

The number of varicella cases in vaccinated persons increased in the first four years of AGV and the proportion of those vaccinated in all reported varicella cases went up from 0.9 to 8.2% [183].

This has changed since 2009, when the number of vaccinated cases as well as the proportion of those vaccinated among all varicella cases began to decrease again (unpublished data). In Munich, the proportion of vaccinated cases among all reported varicella patients increased to 9% until 2009 before remaining stable at 9–10% during the years 2010 and 2011 [223].

Vaccine effectiveness during outbreaks in day-care-settings was generally high (overall 71%) and differed significantly by disease severity and the number of doses administered. Moreover, vaccine effectiveness after one dose differed slightly when compared to the monovalent vaccines [194].

In a time-series analysis, a strong association was found between coverage, number of cases in the one-to-two year-old age group and herd effects in infants. Under field conditions, the vaccine effectiveness of a one-dose vaccination was estimated to be 83.2% [225].

A recent case-control study of paediatric practices in Germany by Liese et al. 2013 [226] also showed the varicella vaccination to have a high effectiveness for up to five years after vaccination in a population with vaccination coverage of about 50%. After adjusting for gender and school/day-care attendance, vaccine effectiveness of one-dose of OKA/RIT against PCR-confirmed varicella of any severity was 71.5% (95% confidence interval [CI]: 49.1–84.0) and 94.7% (95% CI: 77.8–98.7) against PCR-confirmed moderate or severe varicella. Adjusted effectiveness for any varicella vaccine was 86.4% (95% CI: 77.3–91.8) against any severity and 97.7% (95% CI: 90.5–99.4) against moderate or severe varicella. As in the outbreak investigations [194], one of the monovalent varicella vaccines (OKA-/RIT) showed slightly lower vaccine effectiveness (71.5%) against varicella of any severity, but similar vaccine effectiveness (94.7%) against moderate or severe varicella after one-dose vaccination.

Conclusions

- Sentinel results and regional surveillance confirm the large (up to > 75%) decline in varicella morbidity following the introduction of routine varicella vaccination in Germany.
- Data from Germany document a reduction in complications and hospitalisations related to varicella after introduction of varicella vaccination.
- In addition to the direct influence of the vaccine, herd protection is visible, including a reduction of varicella in infants under one year of age.
- Varicella vaccination has so far shown no influence on the epidemiology of HZ in general; age-specific effects in children, adolescents and adults have to be further investigated.
- Acceptance of varicella vaccination has been growing in doctors and parents; the availability of tetravalent vaccine may have played a role in this.
- Cost coverage of vaccination has an impact on vaccine uptake.
- Vaccination coverage of >80% is possible.
- Vaccine effectiveness after two doses is higher than after one dose; several studies raise the concern that one-dose vaccine effectiveness may vary for different varicella vaccines, but further studies are needed. Vaccine effectiveness differs with regard to the severity of varicella.
- Surveillance has to be continued.

Italy

In Italy, the current National Vaccination Plan 2012–2014 does not recommend universal vaccination in infancy and postpones the introduction of universal vaccination to 2015. It does, however, recommend a two-dose schedule in susceptible adolescents 11–18 years of age. Vaccination is also recommended for other high risk subjects (such as susceptible women of childbearing age, healthcare workers, and persons living in the same household as immunocompromised individuals). Nevertheless, eight of 21 regions have – some very recently – introduced universal vaccination in their childhood immunisation program. Additionally, an Interregional Group on Varicella Vaccination has been established in June 2013 in order to assess the effectiveness of the programmes started in these regions, providing a standardised method to collect data from regions that have already started a universal varicella vaccination programme [updated from the public consultation].

The universal vaccination programme started in Tuscany in 2008, and after three years of implementation the annual incidence rate of varicella decreased from 2/1 000 to 1/ 1 000 persons. In 2011, vaccination coverage at 24 months with MMRV vaccine had reached 82.2%. Hospitalisation rates decreased in all age groups. These data were published by Becchini et al. in 2014 [230].

In Sicily, the vaccine has been universally administered since 2003 to two-year-old children, with a catch-up dose at 12 years of age in susceptible adolescents. The coverage rate for children born in 2005 was 70.0%, while that for susceptible adolescents born in 1995/1996 was 45.1%. Annual incidence rates of varicella declined from 95.7 for 1 000 person-years in 2004 to 9.0 for 1 000 person-years in 2007 [184].

Veneto introduced universal vaccination in 2005 for children aged 14 months, with a second dose for six year-old children and a catch-up dose for teenagers. The average adjusted adherence rate was 8.1% in the cohort of children born in 2004, 59.9% in the 2005 cohort and 70.0% in the 2006 cohort, showing an increase in acceptance of the vaccination. However, it is still too early to observe the effect of the new vaccination schedule [76].

No data are available for the other regions.

Conclusions
- Rapid reduction of the incidence of varicella in Sicily and reduction of both incidence and hospitalisation rate in Veneto.
- At current there are no data available relating to the impact on zoster.

Spain

Spain selectively vaccinates all susceptible teenagers at 10–13 years of age; the exact age is chosen by the autonomous communities. Two autonomous communities (Madrid and Navarre) and two autonomous cities (Ceuta and Melilla) run universal childhood vaccination programmes, with coverage rates over 90% (see schedules in Table 1). In the remaining Spanish regions, varicella vaccination is carried out by private practice, and coverage ranges between 12% and 64% (average 32%) [public consultation]. Regarding current vaccine availability in Spain, the Spanish Agency of Medicines and Health Products banned Varivax from purchase at most Spanish pharmacies in 2014. Varilrix is approved for hospital use only [updated by public consultation] [231].

In Madrid [232], universal vaccination began in November 2006 with a one-dose schedule at 15 months. Vaccination coverage for the period 2007–2009 was 92.7. Between 2006 and 2009, the incidence rate of varicella dropped from 718 cases per 100 000 inhabitants to 162 per 100 000 inhabitants (-77%) [232]. Hospitalisation rates were 4.52/100 000 population for the period 2001–2003, 4.84/100 000 for the period 2004–2006 and 2.49/100 000 for the period 2007–2009 (138). The programme was withdrawn in November 2013.

In Navarre [233], a universal vaccination programme was started in 2007, with a two-dose schedule at 15 months and three years, and a catch-up at 10 years (for those susceptible). Previously, in 2004 and 2006, all persons born between 1990 and 1996 and considered susceptible were vaccinated. Vaccination coverage for varicella in 2009 was 95% for the first dose and 81% for the second one.

A recent study published by García Cenoz in 2013 [199] assessed data up to 2012. Between 2006 and 2012, the incidence of varicella in children aged 0 to 14 years decreased by 98.1%, from 50.1 cases per 1 000 inhabitants to 1.0 per 1 000. Children aged one to eight years were the vaccinated cohorts, and their incidence of varicella decreased by 98.5%. Important reductions were also achieved in under-vaccinated groups: 90.5% in infants under one year of age and 89.4% in children aged nine years. Hospital admissions rate for varicella or its complications decreased by 89.0%, and in 2012, there was only one admission of a new-born with neonatal varicella. Vaccine effectiveness for at least one dose was 96.8% (95% confidence interval: 96.3–97.2%).

The very significant reductions are higher than those observed in other studies and are the consequence of a two-dose schedule coupled with a catch-up programme and the very high vaccination coverage achieved [233].

A study published in 2014 by Gil-Prieto [234] reviewing hospital discharges between 2005 and 2010 related to varicella and herpes zoster at the national level showed that severe varicella infections decreased after implementation of varicella vaccination in Spain. Due to the variety of strategies, schedules and coverage in Spain during these years, the study could investigate the potential effects of moderate vaccination coverage in the epidemiology of varicella and herpes zoster (HZ); no significant differences were found in HZ hospitalisation rates in the different regions.

Conclusions

- Rapid reduction of the incidence of varicella and hospitalisation rate in all age groups for both vaccinated and unvaccinated individuals.
- Greater reduction in the region with the two-dose schedule (Navarre).
- Different vaccination coverage rates did not affect the hospitalisation rates of HZ between 2005 and 2010.

Latvia

Universal coverage introduced in 2008 with one dose between the ages of 12 and 15 months.

Greece

Vaccination with one dose has been recommended and available in Greece since 2004. Universal coverage was introduced in 2006 with one dose, and in 2009 with two doses, the first administered between 12 and 15 months of age, and the second between four and six years of age. A study by Cristelis et al. on the impact of vaccination on the epidemiology of varicella and HZ in children in Greece is awaiting publication [public consultation].

Luxembourg

Varicella vaccination targeted at risk groups was introduced in Luxembourg in 2003. Routine varicella vaccination with 2 doses of the quadrivalent MMRV vaccine for all toddlers at 12 and 15-23 months of age was introduced in the national schedule in 2009: after only 2 years, 94.5% of the children are vaccinated with one dose and 83.3 received the 2 recommended doses by the age of 25-30 months, according to the 2012 national vaccine coverage survey [235].

Cyprus

Since November 2010, the varicella vaccination is only recommended (no universal coverage). Two doses are also recommended in Cyprus, the first at 13–18 months and the second at four to six years of age.

6.2 United States experience with varicella vaccination

Prior to licensure of varicella vaccine in the United States in 1995, varicella was an endemic childhood disease which was acquired by nearly all persons. Between 1980 and 1990, the annual estimated incidence of varicella was 15.0 cases/1 000 population, an incidence which resulted in an estimated four million cases per year, a number approximating the birth cohort [236]. More than 90% of cases in the pre-vaccine era occurred in children <15 years of age. During the period 1988–1995, before the varicella vaccine was widely used, there were an estimated 10 632 varicella-related hospitalisations per year, corresponding to a rate of 0.42/10 000 population [237]. During the period 1990–1994, average age-adjusted mortality rates with varicella as an underlying cause of death were 0.41/1 million population, with an average of 145 varicella-related deaths per year (105 deaths with varicella as the underlying cause of death and 40 with varicella as a contributing cause) [238].

The OKA/Merck is the only vaccine licensed in the US. Initial recommendations for the prevention of varicella by the US Advisory Committee on Immunization Practices in 1996 included routine vaccination of children aged 12–18 months of age, catch-up vaccination of susceptible children aged 19 months – 12 years of age, and vaccination of susceptible persons in close contact with persons at high risk of serious complications from varicella [236]. One dose of varicella vaccine was recommended for children aged 12 months–12 years and two doses 4–8 weeks apart for persons 13 years or older.

On a national scale, one-dose varicella vaccination coverage among children aged 19–35 months increased from 26% in 1997 to 90% in 2007 [239,240]. At two US sites conducting active surveillance, varicella incidence decreased by 90% during the period 1995–2005, with reductions in all age groups, including infants <12 months of age and adults, suggesting herd-immunity effects beyond the age groups for whom vaccination was recommended [188]. The number of varicella outbreaks at the two active surveillance sites fell from 236 during 1995–1998 to 46 during 2002–2005 (p<0.001), as did the size and duration of outbreaks [212]. Nationally, the estimated average annual number of varicella-related hospitalisations decreased by at least 65% in all age groups between 2000 and 2006 compared to the pre-vaccination era. This suggests that an estimated 50 000 varicella-related hospitalisations were prevented by varicella vaccination during this period [237]. Varicella-related hospitalisations among 0–4-year-olds, the age-group with the highest hospitalisation rates prior to introduction of varicella vaccine, fell from 2.5/10 000

during the period 1988–1995 to 0.7/10 000 during the period 2000–2006. The majority (70%) of varicella-related hospitalisations in both periods occurred among persons with no co-morbid or immunocompromising conditions that would have predisposed them to severe varicella. Estimated direct medical expenditures for varicella-related hospitalisations and ambulatory care visits on a national scale were 74% lower in 2002 than in 1994 and 1995 [241]. Average age-adjusted mortality due to varicella as an underlying cause of death decreased 88% to 0.05/1 million population during the period 2005–2007 (p<0.001), with a reduction of 97% among persons <20 years [242].

Given that single dose varicella vaccination in children is estimated to be 85% effective (median; range 44–100% in post-licensure studies) [190], approximately 15% of vaccinated individuals may develop varicella if exposed to VZV. Although varicella incidence, especially cases of severe varicella, fell dramatically during the first 10 years of the routine one-dose varicella vaccination programme for children in the United States, varicella in vaccinated individuals was not uncommon. In 2005, with high coverage of one-dose varicella vaccination among pre-school aged children, 72% of reported varicella cases at the two US varicella active surveillance sites were among vaccinated individuals [186]. Varicella in vaccinated individuals was significantly milder, with fewer lesions, shorter duration of rash, and fewer complications. Although less likely to transmit VZV, vaccinated individuals with varicella are infectious [243].

The decline in varicella incidence reached its nadir in 2002, after which incidence remained stable [188,244]. Varicella outbreaks continued to occur, even among highly-vaccinated school populations, although the outbreaks were smaller and less common than in the pre-vaccine era. In response, the United States implemented a routine two-dose varicella vaccination programme for children in 2006, with the first dose administered at 12–15 months and the second dose at four to six years [167]. At the time, trials had shown that a higher proportion of children (~ 99%) achieved an antibody response of $\geq$5gp ELISA units after the second dose of varicella vaccine, suggesting that a second dose would provide protection to the 15–20% of children who do not respond adequately to the first dose [244]. The recommended age of 4–6 years for the second dose of varicella vaccine was chosen so as to harmonise with existing recommendations for MMR vaccine use in the United States. It was supported by the epidemiology of varicella during the mature one-dose programme, with low incidence and few outbreaks among pre-school aged children and higher incidence and more outbreaks among school-aged children.

National data on two-dose varicella vaccination coverage in the United States are limited; data from immunisation registries and school records at the active surveillance sites and in selected States suggest that two-dose coverage among school-aged children (5–12 years) was 30–50% during the period 2008–2010 [245-247]. Although additional surveillance will be needed to fully describe the impact of the routine two-dose varicella vaccination programme, reductions in varicella incidence of 40–50% have been reported by the active surveillance sites and selected States in the first two years since its implementation [216,245].

Monitoring the impact of the varicella vaccination programme on the epidemiology of HZ remains an important priority. Data from one of the active surveillance sites for varicella and from a managed-care organisation demonstrate that children who had received the varicella vaccine had a 4 to 12 times lower risk of contracting HZ than unvaccinated children, although for non-vaccinated children and adolescents 10 to 19 years a trend of increasing HZ incidence [171,248,249] was observed. Baxter in 2013 [172] found lower rates of HZ in a cohort of vaccinated children than in unvaccinated children during the pre-vaccine era.

Overall, HZ incidence in the United States is rising in persons of all ages, but since increases in HZ began before the varicella vaccine was licenced, the increase does not appear to be solely attributable to varicella vaccination [250]. Trends in HZ incidence are difficult to interpret because the risk factors for HZ, other than age and immunosuppression, are poorly understood.

Conclusions

- The US varicella vaccination programme has dramatically reduced varicella incidence and related complications, hospitalisations and deaths.
- Incidence has been reduced in infants <12 months of age and adults, suggesting indirect effects in age groups for whom vaccination was not recommended.
- One dose of vaccine has proved insufficient to prevent outbreaks, as it can lead in 15% of cases to BV cases. Two doses have been recommended since 2006.
- Trends in HZ incidence are challenging to interpret given that the risk factors for HZ, other than age and immunosuppression, are poorly understood.
- Monitoring the impact of varicella vaccine on HZ remains a priority.

7 Insights from modelling

Modelling studies contribute to the understanding of the impact of vaccination programmes. Models provide necessary input about what to expect and are very sensitive to the assumptions used. Models can also incorporate the varying degrees of uncertainty in several parameters (e.g. duration of protection, age contact rate, mechanisms which control HZ developments, etc.). Some parameters (e.g. patients with HZ as source of transmission of wild varicella in the community or endogenous boosting) have not yet been systematically incorporated into models.

7.1 Potential impact of varicella vaccination on the incidence of varicella

Transmission dynamic models have been used to project the impact of varicella vaccination in several high income countries (in Europe, USA, Canada and Australia). Results may depend on the country-specific characteristics (contact mixing and epidemiology). Most of these models are adaptations of an original model by Brisson et al. [251].

Models predict that routine infant varicella immunisation with either a one- or two-dose strategy will cause a rapid decrease in varicella incidence in the first decade after vaccination [94,252-256] [257]. However, a 'post-honeymoon' epidemic is likely to follow, before a new, lower equilibrium level of varicella is reached [94,256].

Most cases occurring in the new equilibrium are likely to be BV cases. BV cases are most likely to occur at intermediate levels of coverage (50-70%) and decline at high coverage levels [258], and they are more frequent if a one-dose strategy is used [259]. One model suggests that the incidence of BV may be higher than reported in clinical trials, partly because in a population setting with high coverage there is less opportunity for vaccine-induced protection to be boosted by natural exposure to varicella [252].

At low coverage levels and/or if a one-dose strategy is used, a post-vaccination equilibrium may never be reached. Instead, epidemics consisting of both natural and BV cases may reoccur at regular intervals [94,252]. The size of these epidemics would be larger and they would be more frequent if coverage is low and/or a one-dose strategy is used [252,258]. However, a vaccination programme with a two-dose strategy at high coverage (>90%) and/or an extensive catch-up campaign in older children (e.g. those aged 12 years) during the first year of vaccination may avoid a 'post-honeymoon' epidemic and achieve a near elimination of varicella disease [94,251,253,256,259]. Catch-up campaigns would have no effect on varicella incidence after achieving a long-term equilibrium [258].

A shift in the average age of infection is predicted, although the absolute number of cases in adults is not expected to increase unless coverage is below 80% [252,253,255,258-260].

A routine adolescent vaccination strategy would have limited impact on natural varicella, even where coverage is high (e.g. 95%), because most adolescents already have natural immunity [251,261]. This approach would not take into account the impact of vaccination on high-risk groups for severe varicella, e.g. women of childbearing age or immunocompromised patients and their healthy contacts. On the other hand, delaying the second dose of a two-dose strategy until pre-school or school age would not have any more impact on the disease than giving it to younger children [252,256,262].

Model results are highly sensitive to assumptions made about age-dependent contact rates [251,252,255,256] and vaccine efficacy [94,251,256,259]. More recent models [252,253,256] have used empirical findings from diary-based surveys of contact patterns [263], meaning that the models reflect varicella seroprevalence data more closely [264]. There is still little evidence relating to long-term vaccine efficacy, particularly for a two-dose strategy [259].

Conclusions

- Results from modelling are country-specific and are highly sensitive to assumptions about age-specific contact rates, vaccine coverage and vaccine efficacy.
- Models predict a sharp decrease of varicella incidence, as already seen through surveillance in countries which have implemented universal vaccination.
- At low-coverage levels and/or if a one-dose strategy is employed, epidemics consisting of both natural and BV cases may reoccur at regular intervals.
- Unless coverage is below 80% the absolute number of cases in adults is not expected to increase.

7.2 Potential impact of varicella vaccination on the incidence of herpes zoster

Several models of varicella vaccination impact assume that contact with varicella cases causes exogenous boosting of specific immunity to zoster [94,252,253,255,256,258] [257]. These models suggest that routine infant varicella vaccination will cause zoster incidence to increase in the medium term. However, in the medium-long term (30–75 years after vaccination), zoster incidence will decrease to levels below what they were prior to vaccination. Higher coverage, higher vaccine efficacy and two-dose vaccination programmes are predicted to produce the greatest medium-term increases, but lower zoster incidence in the long term.

The magnitude of the medium-term increase in zoster incidence is dependent on assumptions made about age-dependent contact rates, the rate of zoster reactivation and the duration of immunity following exogenous boosting [253,256,258,259,265].

Introducing HZ vaccination for older adults may mitigate the effect of infant varicella vaccination on HZ incidence, but only to a very small extent [259,262].

ECDC funded a multi-country model [2,3] that used highly detailed socio-demographic data for every country. The model removed the constraint that the duration of CMI and the reactivation rate are the same in all countries [4].

This model suggests that the short/medium-term impact is country-specific and therefore an increase in HZ is not expected in all countries but rather in countries where HZ rates were milder due to the greater force of exogenous boosting. These findings might provide an explanation for the different conclusions drawn from empirical evidence generated in the literature about the potential effect of mass varicella vaccination on HZ.

Conclusions

- Models are very sensitive to the assumptions used and the uncertainties around these assumptions.
- Most models that assume the exogenous boosting theory predict that universal varicella vaccination will cause HZ to increase in the long medium-term (up to 30–75 years after vaccination).
- One model suggests that the short/medium impact of varicella vaccination on HZ is country-specific.

8 Health economic aspects of varicella vaccination programmes

Health economic evaluations of varicella vaccination have been conducted in Europe, USA, Taiwan, Singapore, Israel and Canada and reviewed in the literature [266-268]. However, the majority of these evaluations use static models rather than transmission dynamic models. Dynamic models are more adequate than static models for capturing the full range of effects of vaccination relevant to economic evaluations, including indirect protection (herd immunity), shifts in the age of infection and (potentially) the boosting of immunity to zoster [265,267]. A few models also took into account potential waning of vaccine protection.

New information on parameters related to the vaccine or to the mechanisms of HZ development may result in additional costs. For example, additional costs could arise if new findings would result in a need to protect more adults (or adults at high risk, e.g. vaccinated women of childbearing age) after childhood vaccination.

Studies examining varicella outcomes alone mostly suggest that infant varicella vaccination (12–24 months) with one or two doses is cost-saving from a societal perspective, even when the potential detrimental effect of zoster boosting is taken into account [266-268]. Catch-up programmes targeted at susceptible children in their second year of life may also be cost-effective.

The majority of cost savings involve the prevention of indirect societal costs (time off work due to sickness or to care for children with varicella). From a healthcare perspective, the cost savings following vaccination are smaller and consequently only a few studies suggest that vaccination is cost-effective. However, early childhood vaccination may still be cost-effective (i.e. the net cost of the intervention is good value for money due to the health benefits generated) even if loss of immunity to zoster is not assumed. In addition to these factors, assumptions about vaccine cost and effectiveness are influential in determining the results of evaluations.

Only a few economic evaluations incorporate the potential effect of boosting immunity to zoster, and these are much less optimistic [261,269,270] [257]. In the medium term, following early childhood vaccination (with or without a catch-up programme for older age groups), a net deficit in both healthcare costs and quality-adjusted life years is expected. This means that the increase in morbidity and healthcare costs due to zoster outweighs the decrease due to varicella vaccination. However, in the longer term (>50 years) there may be net medical cost savings and health improvements. Hence, the cost-effectiveness of vaccination is dependent on the time horizon and discount rate used in the analysis. If long-term outcomes are considered, then vaccination can be cost-effective

Vaccination targeted at specific subgroups can be realistically evaluated using static models since the dynamic effects (herd immunity and reduced boosting of HZ resistance) of these limited programmes are likely to be small. Hence vaccination targeted at susceptible adolescents may be cost-effective since it would have a much milder impact on zoster incidence [261]. Vaccination of susceptible pregnant or postpartum women following anamnestic and serological screening appeared to be cost saving [271,272], although vaccinating against varicella in pregnancy is currently contraindicated. Vaccination programmes targeted at healthcare workers may be cost-effective from an employer's perspective [267]. Vaccination of children prior to organ transplant was highly cost-effective from both hospital and societal perspectives [273,274]. Vaccination of young immigrants may be cost-effective if they are children under five years old, or if serological testing is used to identify those susceptible [275,276].

Conclusions

- Health economic evaluation models have mostly used static models that do not take into account dynamic effects as herd immunity, shift in the age of disease or the boosting hypothesis.
- New information on parameters related to the vaccine or to the mechanisms of HZ development may result in additional costs.
- The majority of cost savings occur by preventing indirect societal costs (time off from work due to sickness or to care for children with varicella).
- If the boosting hypothesis is taken into account, the increase in morbidity and healthcare costs due to zoster outweighs the decrease in varicella over a period of up to 50 years, when net medical cost savings may occur.
- Evaluation of vaccination targeted to specific subgroups can be realistically conducted with static models (susceptible adolescent, healthcare workers or children prior to organ transplant) and may be cost-effective.

9 Follow-up and monitoring of varicella vaccination programmes

Implementation of routine varicella vaccination should be accompanied by monitoring to assess its impact.

Essential elements of monitoring include vaccine coverage, vaccine effectiveness, occurrence of adverse events, age-specific varicella disease severity and age-specific varicella incidence, HZ cases and hospitalisations. Ideally, this data should be collected before a varicella vaccination programme is introduced, in order to evaluate the year-to-year variation of varicella in the unvaccinated population, and to detect a rise in HZ which may have already started before a varicella vaccination programme was introduced (i.e. not attributable to varicella vaccination.)

To evaluate the (long-term) impact of routine varicella vaccination, information on vaccine coverage is needed – preferably by dose. It is very important to achieve sufficiently high coverage as this will have an increased impact on disease occurrence. As result of reduced virus circulation and less booster opportunities, the age of infection may increase. Nevertheless, with high coverage an increase in age-specific incidence, and therefore an overall increase in the severity of the disease, will be avoided. However, medium, or low coverage might lead to undesirable effects (increased age of infection, linked to a higher frequency and increased severity of varicella infection).

Information on vaccine coverage can be obtained from immunisation registers, if available, otherwise by regularly measuring vaccination uptake or, if neither means are available, by collecting information on the number of doses sold.

Another way to address the issue of long-term impact could be to monitor vaccine coverage and age-specific disease occurrence – preferably for both milder and more severe disease – and to monitor median age of infection and potential changes in this median age. An additional means of assessing longer term effects is to perform regular seroprevalence studies. In the pre-vaccination era, a steep rise was seen in seroprevalence at an early age, reaching high levels in adolescents. Changes to this age-specific seroprofile together with disease surveillance could inform countries on (future) changes in age-specific infection dynamics which are directly associated with changes in age-specific disease dynamics. Ideally, population-based sera collection or more readily available residual sera could be considered for conducting seroprevalence studies.

While aggregated data on age-specific disease occurrence and vaccine uptake are essential, collecting information on disease severity and sequelae stratified by age and vaccination history is also strongly recommended. This will offer insight into the occurrence of vaccinated BV cases in relation to overall changes in severe disease after the implementation of routine vaccination.

Given the uncertainty in the mid-to-long term (less booster opportunities) regarding the occurrence of HZ among cohorts not yet eligible for VZV vaccination, surveillance of HZ incidence is highly encouraged. The decrease in booster opportunities may lead to a greater risk of reactivation resulting in HZ, but the role of external viral exposure to VZV immunity remains controversial.

Monitoring must also include an evaluation of adverse events, in particular information on severe adverse events following vaccination.

With regard to disease surveillance sources used to monitor impact, sentinel systems based on physicians' consultation and hospital admission data are useful both for varicella and HZ diseases. This surveillance (using clear case definitions) needs to be established before implementing routine varicella vaccination in order to evaluate the potential impact. National databases of mandatory notifications, hospital discharge codes and mortality are also relevant sources.

Conclusions

- Surveillance systems must be established to evaluate the effect of a potential vaccination programme, ideally before the vaccination programme starts.
- The key elements to survey should be vaccine coverage, vaccine effectiveness, occurrence of adverse events, age-specific disease incidence of varicella and HZ and age-specific incidence of severe disease (i.e. needing hospitalisation).
- Sources could be sentinel systems, hospital admissions/discharge codes or mandatory notifications.
- Surveillance for zoster is needed to assess impact of varicella vaccination on HZ.
- A potential system for HZ surveillance must be a long-term effort as, according to modelling data, the impact on HZ may only be visible after 10–15 years or more.

10 Discussion

Seroprevalence of varicella

Findings from the different seroprevalence studies included in this review indicate that VZV is a common childhood disease in all EU/EEA countries for which data are available. Antibodies to VZV are generally acquired below the age of 10 years and by young adulthood the majority of individuals are seropositive for anti-VZV antibodies.

However, antibodies are acquired at a much earlier age in some countries than in others. This has been partially attributed to the varying use of day-care and pre-school facilities and different social contacts.

Most neonates are seropositive at birth, probably due to the presence of passively acquired maternal antibodies. Further monitoring is required to determine whether protection to children from vaccinated mothers is lower than from mothers that have experienced natural varicella.

Incidence of varicella and force of infection

In the absence of vaccination, the annual number of varicella cases in a country is close to a country's birth cohort. Studies reporting on the incidence of varicella disease in EU/EEA countries confirm that varicella is primarily a childhood infection, however the incidence of varicella per age group was found to vary, depending on the country or region.

Additionally, variability was found in the force of infection and herd immunity thresholds among EU/EEA countries, pointing to the fact that VZV transmission may be sensitive to differences in mixing patterns, especially in the younger age groups.

These regional differences found in the burden of varicella in the EU/EEA (seroprevalence, incidence and force of infection), as well as the particularities of specific groups such as healthcare workers, women of childbearing age and people born in non-EU countries, should be taken into account when assessing recommendations on varicella vaccination at country level. They will also have important implications for the design and implementation of a VZV vaccination programme.

Healthcare utilisation due to varicella disease

In the current review, the standardised annual incidence of hospitalisations due to varicella was reported to range from 1.9–5.8 per 100 000 population. The hospitalisation rates were found to vary depending on the country or region, age group of the cases (rates decreased with age in all countries) and presence of other underlying conditions.

The median length of hospital stay was found to vary between three and nine days, and duration was found to be dependent on age (longer for adults than for children) and the presence and type of complications.

It is important to mention that the incidence of hospitalisations due to varicella in the EU/EEA countries has to be compared very carefully as there are significant differences in the study design and method of estimation. Additionally, hospitalisations will depend on the age of infection with varicella among the countries, as the severity of varicella hospitalisations is known to increase with age.

Varying health-seeking behaviours and the different structure of healthcare systems across countries may also have an impact on the incidence and duration of hospitalisation. It should be up to individual countries to understand their own baseline hospitalisation rates (and healthcare use in general, including general practitioners) so they can monitor rates after the introduction of varicella vaccine and improve their understanding of the impact of the vaccination programme on disease burden in their country.

Complications of varicella disease

Varicella is commonly a mild disease; however 2–6% of varicella cases attending a general practice are estimated to develop complications. The most frequent complications reported are skin and soft tissue superinfections, followed by neurological and pulmonary complications. The type and severity of these complications were reported to vary among populations and age groups.

Although there is a greater risk of complications for infected neonates, adults, pregnant women or those who are immunocompromised, it is important to flag up that most complications and hospitalisations for varicella reported in the literature occurred in children who were immunologically healthy, with no underlying medical conditions.

Severe varicella is more frequently reported in children simply because varicella is mainly a childhood disease. However, it has consistently been demonstrated in the literature that the risk of severe varicella and complications

is high in infants and after adolescence, but also increases with age. Therefore it is important to monitor the impact of varicella vaccination on the mean age of varicella infection.

Varicella-related mortality

The risk of death from varicella was found to be low, with case fatality ratios varying from 0.01% to 5.4% among hospitalised cases of varicella.

The risk increases dramatically with age, as subjects over 15 years had a 16–30 fold greater risk of dying than children aged 1–4 years, indicating the need to monitor a potential increase of infection age for varicella following vaccination.

Underlying conditions were found to be present in about 20–30% of cases, the most common being immunosuppressive disorders such as acute lymphoblastic leukemia (ALL) or other blood disorders, however most of those who died of varicella were reported to be previously healthy individuals.

Varicella vaccines efficacy and immunogenicity

The first varicella vaccine was developed in 1974 in Japan from a strain isolated in a clinical specimen and attenuated through several passages in cell culture (OKA strain). Several monovalent and combined varicella vaccines are currently authorised in Europe.

Efficacy and immunogenicity results confirm that monovalent and combined varicella vaccines are highly immunogenic and efficacious in preventing varicella disease, as demonstrated in controlled clinical studies in healthy subjects. Efficacy is very high against severe varicella and lower against less severe varicella.

A two-dose vaccination regimen results in higher seroconversion rates and vaccine efficacy, compared with a single-dose administration. A second dose given 6–12 weeks after primary immunisation elicits comparable antibody responses to those following administration of a second dose at 3–6 years, however the optimal timing of the second dose is still under discussion (see 'Post-marketing studies on varicella vaccine effectiveness' section below).

Other uncertainties remain concerning the duration of immunity, the risk of complications in BV cases many years after vaccination, the need and optimal timing for additional booster doses and the long-term effects of varicella vaccination (e.g. maternal antibody levels in new-borns from varicella-vaccinated mothers.)

Varicella vaccine safety

Monovalent and combined varicella vaccines are generally well tolerated, except for an increased risk of one additional febrile seizure every 2 600 to 2 700 vaccinations after a first dose of a combined MMRV vaccine at age 12–23 months compared with separate MMR and V administration.

Febrile seizures are not uncommon in young children and generally have an excellent prognosis, although some require hospitalisation and they are distressing to parents [277]. A second dose of MMRV is less likely to cause fever. Also, for those countries choosing a long interval between doses schedule, rates of febrile seizure are lower in children aged 4–6 years than in infants aged 12–15 months [233].

Taking this into account, the US Advisory Committee on Immunization Practices (ACIP) does not express a preference for use of MMRV vaccine over separate injections of equivalent component vaccines (i.e. MMR vaccine and varicella vaccine –MMR+V-) [277]. However, practices in the USA [177] and in Germany recommend separate application of MMR and varicella vaccine for the first dose. It appeared later that these separate injections resulted in a reduction of up to 12% in varicella coverage in Germany [175].

A study published by Hambidge in 2014 reports that delaying MMR vaccine past 15 months of age (to 16 to 23 months) results in a higher risk of seizures. The correlation is twice as strong for the MMRV vaccine [278].

WHO recommends considering routine childhood immunisation against varicella where the disease is a relatively important public health and socioeconomic problem, where the vaccine is affordable, and where high and sustained vaccine coverage (≥ 80%) can be achieved [217]. The use of MMRV has the advantage of providing two vaccines in one visit and may help reach high vaccination coverage.

Post-marketing studies on varicella vaccine effectiveness

The impact of vaccination programmes has to be analysed carefully. Post-marketing studies on varicella involving a one-dose schedule, low vaccine coverage, or two-dose programmes could be confounded through periodic exogenous exposures. This issue has also been raised by modelling studies, which predict that BV incidence may

be higher than reported in clinical trials because in a population setting with high coverage there is less opportunity for vaccine-induced protection to be boosted by natural exposure to varicella.

When planning a varicella vaccination programme, several aspects need to be considered: the type of vaccine (monovalent/tetravalent or vaccine brand), the number of doses, the interval between doses, the vaccination age, and the vaccination strategy.

Monovalent and tetravalent vaccines are available and have proven to be efficacious and safe. The latter vaccine has proven to be more beneficial in reaching a higher vaccination coverage, as varicella is simultaneously administrated with MMR in one injection. The most relevant point of concern is the increase of febrile convulsions following a first dose of the tetravalent vaccine during the second year of life (one for every 2 300 doses). No increased risk was observed following a second dose.

In order to eliminate measles in all countries of the WHO European Region, a vaccination coverage above 95% with two doses of a measles-mumps-rubella vaccine in all population groups and in all geographical areas is required. A varicella immunisation programme should take this goal into account. The existing schedule and high coverage for MMR provides an excellent opportunity to also achieve a high coverage for varicella. On the other hand, any potential detrimental effect on MMR coverage due to the inclusion of varicella vaccine (as MMRV or MMR+ V during the same visit) should be monitored and avoided.

Overall, it appears that the immunogenicity and vaccine effectiveness is higher for some brands of varicella vaccine compared with others, especially when a one-dose schedule is used.

A second consideration when planning the implementation of a varicella vaccination programme is the recommended number of vaccine doses. Most studies on one-dose schedules show a decrease of the burden of varicella, but one-dose schedules fail to fully control outbreaks. For both MMRV and MMR+V, a two-dose vaccination regimen results in higher seroconversion rates and vaccine efficacy. It has been widely shown in the literature that two doses provide further reduction in the burden of varicella and effective control of the disease. Additionally, one-dose varicella vaccination strategies reportedly show an increase in the median age of patients during outbreaks (from six to nine years). There were no data available on outbreaks with two-dose schedule strategies.

The optimal timing of the second dose is still under discussion, but a second dose given 6–12 weeks after primary immunisation elicits comparable antibody responses to those following administration of a second dose at 3–6 years.

Varicella vaccine effectiveness has been estimated at around 85%, leading to a relevant primary vaccine failure; a shorter interval between doses could avoid cases of BV, especially when the disease is not under full control and the wild virus still circulates broadly. However, as mentioned before, in areas where wild-type virus still circulates, natural boosting could be an important factor for reducing secondary vaccine failure. Other important aspects, like the current immunisation schedule in the country, should also be taken into account. Currently, different vaccination schedules are being used (i.e. shorter intervals in Germany, longer ones in Italy), as countries have taken advantage of their existing recommendations for MMR vaccines to administrate the varicella vaccines at the same time [279]. In the US, the schedule of the second dose at 4–6 years was decided based on the low incidence and few outbreaks among pre-school aged children as opposed to higher incidence and more outbreaks among school-aged children during the one-dose programme.

Varicella during the first year of life has been shown to predispose to HZ development because infants have not developed adequate VZV-specific CMI. Therefore exposing infants to the virus strain used for vaccines could also lead to HZ development, and this could be relevant for the advised age at vaccination. More clarity needs to be brought to this area. Recent studies in the USA have not shown an increase of HZ in vaccinated children. Additionally, the vaccine has proved more immunogenic in children up to 12 years than in adolescents and adults; however a second dose significantly increased the response rates in all groups.

Another topic of concern is time since vaccination. A study from Baxter in 2013 [172] showed no waning on the effectiveness of the vaccine over a 14-year period. A review from Bonanni 2013 [209] has shown no consistent trend between BV rate and time since vaccination.

With regard to vaccination strategies, a targeted approach to risk groups and susceptible adolescents would control the disease in some groups where varicella is more serious, but would neither have an impact on the burden of varicella nor on the transmission of the wild virus. Vaccination of susceptible healthcare workers should be encouraged as transmission of disease in these settings may affect populations where varicella is more severe.

Overall, the vaccination of risk groups is plagued by one problem: actually reaching these populations. Reaching adolescents is also challenging as they do not have much contact with health services at this age, unless a school vaccination programme is in place; on the other hand, these strategies have shown to be cost-effective.

A universal childhood vaccination programme with one dose has proved to reduce the burden of varicella disease, but not of BV. A universal programme with two doses has shown to further reduce the burden of varicella and provide full control of the disease. If a universal programme is considered, WHO recommends that countries where

varicella is an important public health and socioeconomic burden should assess whether adequate resources can be allocated to implement varicella vaccination in a routine childhood immunisation schedule to achieve and maintain high coverage levels (> 80%).

Varicella vaccine recommendations in Europe

Varicella vaccine recommendations in the EU/EEA are heterogeneous: only five countries universally recommend varicella vaccination for children at national level and two at regional level.

Some countries have reviewed the recommendations for a vaccine against varicella but decided not to recommend universal vaccination.

For example in France, the Haut Conseil de Sante Publique (French High Council for Public Health) re-evaluated the recommendations for a vaccine against varicella in 2007. After considering data from the US, epidemiological and modelling data, data available on vaccines and data on potential acceptation in France it decided not to recommend universal vaccination[1].

Similarly, from 2007 to 2009, the Joint Committee on Vaccination and Immunisation (JCVI) in the UK considered the potential use of varicella and HZ vaccines in UK vaccination programmes[2]. After reviewing epidemiology data from sentinel GP network and seroprevalence studies and mathematical modelling and cost-effectiveness studies, a universal varicella vaccination for children was not recommended. This decision will be reviewed in light of emerging data on the epidemiology of varicella and HZ infections and the cost-effectiveness of vaccines against these infections.

Sixteen countries recommended nationwide vaccination for susceptible teenagers and/or susceptible risk groups only.

Public health impact of varicella vaccination

Surveillance in the EU/EEA and in USA has shown a rapid reduction in the incidence of varicella, varicella complications, hospitalisation rates and deaths in countries where routine varicella vaccination has been introduced. Incidence has been reduced also in infants <12 months and adults, suggesting indirect effects in age groups for whom vaccination was not recommended.

USA, Germany and the Navarre region of Spain have reported improved vaccine effectiveness when administering two doses instead of one. Effectiveness may differ for different varicella vaccines and is greater for severe varicella.

There has been no increase so far in the absolute number of varicella cases in older age groups compared to the pre-vaccination period. A relative increase in the age of infection has been reported, due to the reduction in cases among younger children, but incidence of severe disease has not increased.

Varicella disease has shown to decline even in areas with moderate vaccine coverage. However, because suboptimal coverage rates (< 80%) could result in an increase of varicella incidence in older ages, WHO recommends varicella vaccination to countries which can reach a vaccination coverage of 80% or above [217]. If universal vaccination fails to result in high coverage, catch-up strategies in adolescents could avoid a shift in the epidemiology of the disease. Good acceptance of the varicella vaccine leading to high coverage has been shown in several countries which introduced universal vaccination, yet the reasons for this success could be country specific and influenced by the affordability of the vaccine and/or the reimbursement practices. On the other hand, in countries where the vaccine is available for purchase in the private sector, but not included in the national immunisation programme, adherence to the vaccine is often high and vaccine coverage reaches a significant portion of the population, though not 80%. These situations should be monitored, as they could also lead to a shift of the disease to older ages.

Some very recent surveillance studies have demonstrated a decline in HZ incidence among cohorts of varicella-vaccinated children, but also suggest a trend of increasing HZ incidence in older, unvaccinated children.

Studies that did not find an increase in HZ incidence following introduction of varicella vaccination were Jumaan [280], in the general population, and Baxter (2013) [172], in vaccinated children followed for 14 years in the US. Other studies found an increase in HZ incidence, starting even before the implementation of the vaccination programme, which makes the effect of vaccination on the epidemiology of HZ difficult to interpret; Tanuseputro [281] and Hales 2013 [282] found a rise in individuals over 60 and 65 years of age, respectively, and Leung [250] and Chao [283] observed an increase in the general population.

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[1] http://www.hcsp.fr/explore.cgi/telecharger/hcsp049r20070816_Varicelle.pdf

[2] http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_133599.pdf

To date, there is no clear evidence of the overall influence of varicella vaccination on HZ epidemiology. Trends in HZ incidence are challenging to interpret, given that the risk factors for HZ, other than age and immunosuppression, as well as the immunological mechanisms involved, are poorly understood. Monitoring the impact of varicella vaccine on HZ remains a priority. Further studies are necessary to confirm the influence of varicella on HZ in unvaccinated groups.

Insights from modelling

Modelling studies contribute to the understanding of the impact of vaccination programmes when epidemiological data are not available.

Overall, models on the impact of varicella vaccination in the epidemiology of varicella predicted a decline of varicella cases following introduction of vaccination, which is in line with published surveillance data from countries using the vaccine.

Models predict that vaccination programmes with a two-dose vaccination strategy with high coverage (> 90%) may achieve the near elimination of varicella disease, even if the wild-type varicella virus will remain in the population for a longer period.

Regarding the impact of varicella vaccination on the epidemiology of HZ, most models which assume the exogenous boosting theory predict that universal varicella vaccination will cause HZ to increase in the medium-long term (up to 30–75 years after vaccination). However, models rely on assumptions, and it is often difficult to correctly estimate model parameters due to lack of available information. In addition, different models weigh factors and uncertainties differently and thus produce different results, for example on the country-specific nature of the impact of varicella vaccination on HZ in the short and medium term. Most models are based on the exogenous boosting theory, disregarding other approaches such as endogenous boosting or wild varicella transmission through HZ.

The uncertainty in model predictions mirrors the unknowns surrounding several parameters related to the vaccine, to the contacts in the population, or to the mechanisms behind HZ development. This challenges both the epidemiological interpretation and the mathematical modelling. At present, the hypothesis of the impact of universal varicella vaccination on HZ comes from mathematical models that need to be considered in the context of the available epidemiological data. More accurate estimations can only be produced if more information becomes available.

Health economic aspects of varicella vaccination programmes

Health economic evaluations of varicella vaccination programmes are heterogeneous and highly dependent on key model assumptions. In particular, they are dependent on the existence of an exogenous boosting of immunity to HZ, the perspective of those evaluating (healthcare provider or society), and the time horizon applied. Uncertainties with regard to the vaccine and the mechanisms of HZ development lead to a disregard of potential additional costs. Additionally, societal impact often depends on the situation in a particular country.

The majority of cost savings due to varicella vaccination occur as a result of preventing indirect societal costs (time off from work due to sickness or to care for children with varicella). From a societal perspective, infant vaccination is likely to be cost-saving, even when the detrimental effect of zoster boosting is taken into account.

Often, the vagueness of cost effectiveness studies is associated with the unclear influence of varicella vaccination on HZ epidemiology. As a matter of fact, when economic evaluations incorporate the effect of external boosting of immunity to zoster, the increase in HZ morbidity (and associated healthcare costs) outweigh the decrease in varicella morbidity in the medium term. However, in the long term (> 50 years), net medical cost savings and health improvements may occur.

Several targeted vaccination strategies for specific groups have been evaluated, since this can be done realistically using static models, and in general these campaigns appear to be cost-effective.

Follow-up and monitoring of varicella vaccination programmes

Surveillance systems are necessary to monitor the effect of a potential vaccination programme.

The surveillance systems for varicella and HZ in the EU/EEA are highly heterogeneous and in several countries there are no surveillance systems for varicella. Most European countries do not have a surveillance system for HZ.

Additionally, vaccination coverage data are missing in several countries which have adopted varicella vaccination recommendations. Valid vaccine coverage estimates, especially in relation to risk groups, are key prerequisites for documenting the performance of national vaccination systems.

Surveillance of varicella and HZ, preferably before implementing a varicella vaccination programme, is needed in order to assess the impact of varicella vaccination on both diseases.

The kind of system required will depend on the aim of the programme, however the key elements to survey should be vaccine coverage, occurrence of adverse events, age-specific disease incidence of varicella and HZ and severity of disease.

A potential system for HZ surveillance must be long-term, as the impact of varicella vaccination on HZ may not be visible for 10–15 years or more according to modelling data.

Additional years of surveillance will be needed to fully describe the impact of the current programmes.

11 Conclusions

The varicella zoster virus continues to cause a high number of varicella cases, potentially requiring medical visits or hospitalisations and occasionally leading to long-term sequelae or even death.

There is growing evidence that varicella vaccines are highly immunogenic, efficacious and safe in preventing varicella disease. Evidence from countries that have implemented universal varicella vaccination of infants demonstrates a significant and sustained decrease in the burden of varicella, with no apparent increases in HZ to date. However, there is no conclusive evidence of the influence of varicella vaccination on HZ epidemiology. Although an increase in HZ incidence has been observed in countries with universal VZV vaccination programmes, the increase seems to precede the commencement of these programmes.

When planning to introduce a national varicella vaccination strategy, aspects such as vaccine type, vaccine strategy or number and timing between doses should be assessed. Groups where disease is more severe (infants, pregnant women, adults, immunocompromised individuals) should be a priority. A universal childhood vaccination programme with one dose has proven to reduce the burden of varicella disease, however BV will still occur.
A universal programme with two doses has shown to further reduce the burden of varicella and provide full control of the disease. If a universal programme is being considered, high coverage levels (> 80%) should be achieved in order to avoid a shift of the disease to older ages. These programmes are cost-effective if there is no associated increase in HZ incidence, and cost saving from a societal perspective. However, when assuming the exogenous boosting hypothesis, models predict a net increase in morbidity and in healthcare costs for up to 50 years in some countries, followed by a decrease.

There are differences in incidence and force of infection in the EU/EEA, which should be taken into account when assessing recommendations for introducing a varicella vaccination programme at country level, as they will have important implications for the design and implementation of a VZV vaccination programme. Additionally, countries should assess their individual epidemiological and socioeconomic situation as well as the capacity to achieve high vaccination coverage.

Mathematical models have shed some light on current gaps. Their value will increase as more evidence becomes available to refine the assumptions on which they are based.

Monitoring the impact of varicella vaccination programmes on the epidemiology of HZ remains an important priority. Good surveillance systems which provide knowledge of historical trends in HZ incidence and post-herpetic neuralgia are of utmost importance. Additionally, and to help interpret HZ trends, there is a need to increase the understanding of the immunological mechanisms behind HZ development.

Knowledge gaps still exist: better pre- and post-vaccination surveillance as well as epidemiological research is needed so that the implementation of a vaccination programmes can be based on informed decisions.

Knowledge gaps include:

- Duration of vaccine-induced immunity beyond 14 years
- Optimal time for a second dose
- Potential need for further doses later in life
- Impact of vaccine coverage on the long-term epidemiology (i.e. shift to older ages) of the disease
- Severity of BV with an increase in time since vaccination (including BV outcomes in previously vaccinated pregnant women)
- Risk of an increased number of complications due to varicella following shifts in the mean age of infection after vaccine introduction (including congenital and maternal varicella)
- Immunological mechanisms for HZ development
- Impact of varicella vaccination on HZ incidence, especially in unvaccinated individuals

Annex

New evidence on 'burden of varicella in Europe'

Search in PubMed

1 September 2010 to 8 June 2012

Total of 198 records, reviewed title of all

Selected 20, review abstract

Read full article of five

Included: two

Fernandez-Cano, Vaccine 2012

The susceptibility of healthcare workers to varicella was 7.45% (95%CI: 7.14 to 7.75). Healthcare workers born after 1980 were twice (95% CI: 1.2 to 3.2) as likely to be susceptible to varicella than those born before 1965.

GUIDO, Journal of Clinical Virology 2012

The prevalence of varicella susceptibility among pregnant mothers was 10.6% (n=539 samples). The prevalence of IgG antibodies increased significantly with age, from 62.5% in the age group 15–19 years to 94.4% in the age group 40–49 years.

Search in Embase

2011–2012 plus the string in the guidance

Filter: human, major clinical studies, control study, chickenpox

123 results

Total of 11 selected for further reading abstract/full text

Six repeated from Pubmed search/five to check if already included in the systematic review or pertinent (R7-R11)

After reading abstract, two selected for reading the full article.

Hospitalisation due to varicella in the Netherlands (p. 47)
van Lier A, van der Maas NAT, de Melker HE, Rodenburg GD, Sanders EAM
BMC Infectious Diseases 2011, 11 Article no. 85

From a representative sample of varicella admissions in the Netherlands, complications were recorded in 76% of the patients. Bacterial super infections of skin lesions (28%), dehydration (19%), febrile convulsions (7%), pneumonia (7%) and gastroenteritis (7%) were most frequently reported. In a third of the hospitalised cases with complications, severe complications occurred.

How frequent is varicella-associated pneumonia in children?
Hervás D, Henales V, Yeste S, Figuerola J, Hervás J.
European Journal of Clinical Microbiology and Infectious Diseases 2011 30:3 (435-437)

More clinical approach to incidence in children hospitalised with varicella of bacterial pneumonia (53%), viral pneumonia (41%) and varicella pneumonitis (6%).

In adults, varicella pneumonitis is the most important cause of morbidity and mortality in adult varicella.

Modified tables from Pallas systematic review

Table A. Seroprevalence of varicella in healthcare workers or medical students in Europe

Country	Author/year	Year	No.	Type of workers	Age group	Outcome
Belgium	Vandersmissen 2000[32]	1996–1997	4923	Healthcare workers	All ages	99%
France	Reignier 2005[33]	2001	251	Healthcare workers	26–62 yrs	99.6%
Germany	Wicker 2007[29]	2005	223	Medical students	20–45 yrs	97%
Italy	Fedeli 2001[31]	1998–2001	333	Healthcare workers	23–60 yrs	98%
Slovenia	Socan 2008[28]	2006	256	Medical students	18–32 yrs	98%
Switzerland	Baer 2005[30]	1999–2003	170	Medical students	22–48 yrs	97%
Spain	Fernandez Cano 2012	2006–2008	2752	Healthcare workers	16–69 yrs 16–25 26–41 42–69	92.5% 12.2 8.1 6.6
				Medical students (interns) Medical staff		5.5 7.6

Table B. Seroprevalence of varicella in pregnant women in Europe

Country	Author/year	Year	Groups	No	Outcome
Finland	Alanen 2005[38]	2000	16–45	558	96%
France	Saadatian 2007[37]	2005	<25 yrs 25–30 yrs 31–35 yrs 36–40 yrs >40 yrs	51 181 181 69 10	100% 99% 99% 97% 100%
Germany	Sauerbrei 2004[6]	1995–1996	16–41 yrs	215	97%
Italy	Guido	2008–2009	15–49 yrs 15–19 yrs 20–24 yrs 25–29 yrs 30–34 yrs 35–39 yrs 40–49 yrs	539 8 48 130 245 120 18	89.4% 62.5% 95.8% 86.9% 87.9% 93.3% 94.4%
Spain	Plan 2007[36] Suárez González 2002[39]	2003 1997–1998	15–24 yrs 25–29 yrs 30–34 yrs 35–49 yrs <25 yrs 22–28 yrs 29–25 yrs >35 yrs	295 386 537 304 39 133 274 59	94% 95% 97% 98% 92% 92% 88% 100%
UK	Talukder 2007[35]	2001–2004	White British women (28 ±6.4 yrs) UK born Bangladeshi (24±4.5 yrs) Bangladeshi-born (26±5 yrs)	1040 in total	93% 95% 85%

a Proportion of positive samples

Records identified through database search and other sources (n=9357)

Records screened (n = 5154)

Full text articles acquired for assessment of eligibility (n = 156)

Records excluded (n = 4998)

Full text articles excluded, with reasons (n = 31)

Full text articles not assessed but may be relevant (n = 25).

New evidence on 'public health impact of varicella vaccination in Europe'

Search in Pubmed

1 September 2010 to 8 June 2012

Search (#11) AND #10 AND ('2010/08/01'[PDAT]: '2012/07/01'[PDAT])

(Same strings as Pallas for varicella and herpes zoster (I) and for objectives 2, 3,4 and 5, with the time limits).

Total of 293 retrieved. After review of all titles and abstracts, six were selected. Following reading of the whole article, one did not include an incidence or a proportion as outcome, so five were included.

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