ECDC PRELIMINARY GUIDANCE

Varicella vaccine in the European Union

The production of this preliminary guidance was coordinated by Paloma Carrillo-Santisteve (OCS/SRS, ECDC), Pierluigi Lopalco (OCS/SRS, ECDC) and Helena de Carvalho Gomes (OCS, ECDC).

The working group on the potential introduction of varicella vaccine was composed of the following experts (in alphabetical order):

Tomas Bergström, Clinical Virology, Sahlgren's University Hospital, Gothenburg, Sweden

Stephanie R. Bialek, Herpes virus Team Lead, Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, USA

Diego van Esso, Paediatrician, Pare Claret Primary Care Health Center, Catalan Institute of Health, Barcelona, Spain

Mark Jit, Public Health England, United Kingdom

Johannes G. Liese, MD, MSc Department of Paediatrics, Paediatric Infectiology and Immunology, University Hospital, Würzburg, Germany

Hester de Melker, National Institute for Public Health and the Environment, Bilthoven, The Netherlands

Zsofia Meszner, National Institute for Child Health, Budapest, Hungary

Heidi Meyer, Paul-Ehrlich-Institute, Langen, Germany

Hanne Nøkleby, MD, Director, Division for Infectious Disease Control, Norwegian Institute of Public Health, Oslo, Norway

Anette Siedler, Robert Koch Institute, Berlin, Germany

Andrea Streng, PhD. Department of Paediatrics, Paediatric Infectiology and Immunology, University Hospital, Würzburg, Germany

This document is a draft and is subject to a public consultation process. The result of that process may lead to changes in the final report.

Suggested citation: European Centre for Disease Prevention and Control. Varicella vaccine in the European Union Stockholm: ECDC; 2014.

Stockholm, April 2014

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
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 and the modelling outputs by a Framework Partnership Agreement (ECDC Grant 2009/002) with Pisa University.

1. Executive summary

1.1 Main findings

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

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

However, in some countries antibodies are acquired at a much earlier age and overall, it has been observed that seroprevalence is marginally lower among children in southern and eastern European countries than in the countries of northern and western Europe. Moreover, countries such as Belgium or the Netherlands report a higher seroprevalence among children under four years than other parts of Europe. This might be attributed to a climate gradient as well as 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 vaccine, varicella continues to cause a high number of cases, potentially requiring medical visits or hospitalisations. Differences in the study design and method of estimation make it difficult to compare the incidence of healthcare use due to varicella in the EU/EEA. Additionally, hospitalisations will depend on the age of infection with varicella (which differs among the countries), as the severity of varicella hospitalisations increases with age.

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 from varicella infections. Most complications, hospitalisations and deaths due to varicella occurred in children who were 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. Higher vaccine efficacy has been reported with two-dose schedules. 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 has been reported, however, MMRV may help achieve a higher vaccination coverage.

Varicella vaccine effectiveness has been estimated at 85%, so breakthrough varicella (BV) cases 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 type of vaccine, number of doses, age at vaccination, as well as possible primary or secondary vaccine failure could have an influence.

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 five 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, due to the decrease in the number of cases in younger age groups.

Mathematical modelling studies predict a decrease in the incidence of varicella following the introduction of the vaccine. These studies also suggest that infant vaccination may be cost-effective if there is no associated increase in herpes zoster (HZ) incidence, and may even be cost-saving if productivity costs are included.

Modelling studies suggest that if exposure to varicella boosts immunity to HZ, then mass infant immunisation may result in an increase in HZ in the medium 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 is country-specific and is only expected in countries where HZ incidence is low due to a higher immunity boosting force.

Health economic evaluations on varicella vaccination programmes show that the majority of cost 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, health care workers, transplant recipients and young migrants) appear to be more cost-effective interventions that do not have a substantial impact on medium-term HZ incidence.

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 and knowledge gaps

Investigations into universal varicella vaccination in children to date have shown it to be highly effective in reducing the burden of varicella disease. However, there is limited knowledge in all of the following areas:

- duration of vaccine-induced immunity;
- optimal time for a second dose;
- potential need for further booster doses later in life;
- impact of vaccine coverage on the long-term epidemiology of the disease;
- severity of BV with an increase in time since vaccination;
- risk of increasing complications due to varicella following shifts in the mean age of infection after vaccine introduction;
- risk of complication in adult BV cases that occur several decades after vaccination and the potential increase in HZ incidence.

These gaps need more research, as they are most likely to influence the decision regarding the implementation of the vaccine.

High vaccine coverage is needed to prevent increase in the absolute number of cases in adults which would lead to an increase in complications. A further important factor to consider is the acceptance of varicella vaccinations by parents and physicians and affordability/reimbursement of the vaccine costs in order to achieve high coverage.

Moreover, differences in the incidence and disease burden of varicella in the EU/EEA, as well as the particularities of some groups (e.g. healthcare workers or women of childbearing age), should be taken into account when assessing recommendations on varicella vaccination at country level. These factors will have important implications for the design and implementation of a varicella vaccination programme.

1.3 Recommendations

While waiting for more evidence on several aspects of varicella vaccination, countries should assess their individual epidemiological and socioeconomic situation as well as the capacity to achieve high vaccination coverage with the vaccine.

Monitoring the impact of varicella vaccination programmes on the epidemiology of HZ remains an important priority. Additionally, there is a need to increase our understanding of the risk factors for the development of HZ and baseline trends in HZ incidence and post-herpetic neuralgia.

Better surveillance systems, as well as a prospective, sero-based study on varicella exposure and quantitative IgG response and HZ incidence could give clarity to some of these uncertainties.

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 and is available for consultation[1].

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, are included in the systematic review and have been published in peer review journals [1-3].

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.

[1] Available by contacting ECDC's Vaccine-Preventable Diseases Programme: vpd@ecdc.europa.eu

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)[4].

Factors associated with VZV reactivation include aging, immunosuppression, intrauterine exposure to VZV and having had varicella at a young age (younger than 18 months) [4], 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 [5]. VZV reactivation and development of HZ may occur as CMI declines with advancing age or other immune-suppressing factors [5-10].

Additionally, CMI may be boosted periodically by endogenous subclinical reactivation of latent virus or by re-exposure to exogenous virus from individuals infected with varicella or HZ [11].

Scientific support for the role of external viral exposure to VZV immunity is inconclusive, with both supportive [12-15] and non-supportive [16] [17] evidence that re-exposure to VZV may be protective against HZ development by boosting CMI. Ogunjimi et al. [18] 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.

Varicella is highly communicable and endemic to all countries worldwide. In temperate climates, 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 [19]. It is more usual in immunocompromised patients and patients over 50 years, and is unusual in children [20].

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 [20]. Lesions can also occur on mucous membranes and cornea [4].

Humans are the only reservoir of the infection which can be transmitted person-to-person by direct contact with respiratory secretions or inhalation of vesicle fluid (airborne spread) [20].

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 [20].

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 [20].

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 [20].

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 [21,22] or VENICE [23] In the EUVAC.NET survey [24], 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 [25]; therefore 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

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 [12,26]. Diverse Enzyme Linked ImmunoSorbent Assay (ELISA) 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 [12].

However, there are differences in the average age of infection between the countries, as antibodies following infection are acquired at a much 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 [12,27-30] than in northern and western Europe [12,31-36]. 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 [12,37]. On the other hand, over 5% of individuals aged 20–29 years were seronegative in Italy, Ireland, Spain and England and Wales [12,26,38].

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 [31,39-41]. In a 2013 study from the Netherlands, protection against varicella was estimated to last 3.4 months for new-borns whose mothers were unvaccinated [42].

None of the studies reviewed reported a significant age-specific difference in seroprevalence by sex. A study by van Lier published in 2013 [43] 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.

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.

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% [44-50]. Seroprevalence figures for medical students were marginally lower (92.4–98%) [47-49] [50] than for healthcare workers (94.5%– 99.6%) [44-46,49]. 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) [49].

Pregnant women

In five [51-53] 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 [54] 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 [55].

Non-EU born/immigrants

In a Dutch study [56], 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 [43] 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 [57] found 85% of pregnant Bangladeshi-born women seropositive compared to 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 a much 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.

The literature review confirmed that varicella cases primarily occur in the younger age groups. The studies included have reported 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) [26].

Reported, standardised annual incidence per 100 000 population ranged from 300–1 291 in western Europe (FR, NL, DE, UK) [32,41] [58-60], to 164-1240 in southern Europe (IT, ES, PT, SI)[29,58,61-71] and 350 in eastern Europe (PL, RO)[72,73]. 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 [63,64,72,74].

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 [74]. This may reflect different contact patterns of children in the various countries.

Data from EUVAC.NET [75] 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.

Pregnant women

Only two studies from the UK have reported on the incidence of varicella during pregnancy [76,77]. 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 [77].

Conclusions

- 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/EFTA countries have reported on the age-specific force of varicella infection (rate at which susceptible individuals become infected) [12,78,79].

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

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 design and method of estimation make it difficult to compare the incidence of hospitalisations due to varicella in the EU/EEA. Additionally, the data also depend on the age of infection for varicella among the countries, as the severity of varicella among those hospitalised increases with age.

Studies from European countries show that standardised annual incidence of hospitalisations due to varicella ranged from 1.9–5.8 per 100 000 population [77,80-83] (unstandardised incidence 1.3–23.06 per 100 000 population) [41,65,74,79,84-88].

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 [69,89], 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 [41,74,79,81,84,86,87,90,91]. According to one study in Spain [87], 58.4% of hospitalisations occur among children <10 years. In the UK, 70% occur in children <15 years [92]. Studies that have reported the incidence of hospitalisation in adults suggest a higher hospitalisation rate in the age range 25–44 years, compared with other adult age groups [74,79,87,88,90], 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 [41,77,81,87,89,91-100]. 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) [93].

According to the country, the incidence of varicella hospital admissions per 100 000 children in those below 15 years was 23 in France [74,98]. In children younger than 16 years it ranged from 6.8 in the Netherlands [101] to 26 in France [84,91] and in Germany it was 14.1 [91] in children <17 years.

EUVAC.NET has published reports on hospitalisations due to varicella for the years 2000–2007 [102], 2008–2009 [103] and 2010 [75]. 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 [75]. 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 [104]. 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 [92] 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[92].

In the Netherlands, a retrospective cohort study found a total of 254 GP consultations per 100 000 population per year [41]. Here too, the incidence of GP-consultations was highest in childhood, with a small peak in incidence among 25–34 years olds (contacts with young children who have high infection frequency).

Conclusions

- In Europe, the incidence of hospitalisations due to varicella per 100 000 population was found to decrease with age in all countries. However, data on varicella case hospitalisation rates is scarce in Europe. Therefore, 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.
- Differences in the study design and method of estimation make it difficult to compare the incidence of hospitalisations due to varicella in the EU/EEA. Additionally, hospitalisations depend on the age of varicella infection among the countries, as the severity of varicella hospitalisations increases with age.

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 [26]. 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 [32,62,67,73,77,84-86,88,91,93,94,96,98-100,105-108]. 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 [107].

Neurological complications are the second most frequent, reported in 4-61% of all hospitalised children [62,65,67,73,77,85,86,88,91,96,98-100,105,109-111]. In Germany, the overall incidence of neurological complications in children ≤16 years of age was estimated as 2.4 per 100 000 population [91,112] (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) [110]. The incidence of meningitis/meningo-encephalitis was reported to be 2.1 per 100 000 population in Slovenia [71], whereas in the Netherlands the incidence of acute cerebellar ataxia is estimated to be 0.25 per 100 000 population [81].

Complications of the respiratory system, especially pulmonary complications have been reported in 3–22% of hospitalised cases [85,91,100]. The main clinical manifestations include pneumonia (due to VZV or other pathogens) and otitis media [65,67,76,88,91,99,106]. In Slovenia, the reported incidence of pneumonia is 0.8 per 100 000 population [71].

Other complications (i.e. gastrointestinal, hepatic and haematological) have been also reported [62,67,91,99,100]. 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) [110].

Long-term sequelae have been reported in 0.4–3.1% of patients hospitalised due to varicella infections [91,96,105] 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 [91]. 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%) [113], at 0–12 weeks gestation with an incidence of 0.4% and at 13–20 weeks gestation with an incidence of 2% [114]. 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 [113]. Moreover, in pregnant women with varicella, there were instances of varicella pneumonia in 10–20% of the cases [115].

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 [116]. Subsequently, the risk of severe varicella is higher in infants and adults than in children [74]. 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 [106] 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 [108].

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 [32]. It has also been observed that neurological complications usually occur in older age groups, whereas severe bacterial superinfections occur in younger age groups[91].

Being immunocompromised is a risk factor for severe varicella [117]. However, most complications and hospitalisations for varicella were found to occur among children who were immunologically healthy with no underlying medical conditions [87,91,96,106,109]. Among 3 632 primary varicella-related hospital discharges in Spain (all ages), 8% had an underlying condition recorded [87]. 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 [101]. 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 [96]. 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 [91].

EUVAC.NET reports incidence data on complications in hospitalised cases due to varicella for five countries in 2008, 2009 [103] and 2010 [75] (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 [65,83,86-88,90,91,95,97,100,104,109,112,116,118,119]. 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) [92]. 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 [74,77,92]. 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 [120].

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) [74,88,89,91,95,116,121].

The common causes of death reported were septicaemia [89,91,95,105,109,116], pneumonia (due to VZV or other pathogens) [88,91,105,116], acute respiratory distress syndrome [91,116], myocarditis [105], endotoxic shock

[95,105] or encephalitis [88,89,95]. Two studies reported fatalities among infants born with congenital varicella syndrome [91,116].

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. In most studies the vaccine gave a high degree of protection, but vaccine failures were registered in those vaccinated, including very young children, children with asthma or eczema, and children treated with corticosteroids, and the incidence of failures increased with the period of time since vaccination.

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 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, Priorix Tetra) 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 [122-124] [125,126]. 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 [Pallas 181, 182]. Further studies compared the protective efficacy following a one-dose with a two-dose vaccination regimen for different varicella-containing vaccines [122-124]. 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 [122]. 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 [123,127]. 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, whereas a titre of ≥50mIU/ml was set as the threshold for a commercially available whole-cell ELISA assay to calculate response rates [128] (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 [129].

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 [130-136].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 [130,132,134,135,137-139]. Moreover, the route of administration (i.e. either subcutaneous or intramuscular injection) had no impact on the immune response [140,141].

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 [134,138,142-144].

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 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% [131]. 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 [145,146].

In an era of external exposure to varicella, antibody persistence was demonstrated for a period of up to nine years post vaccination using a one and two-dose vaccination regimen [122]. 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.

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, the need and optimal timing for booster doses and long-term effects of varicella vaccination (e.g. maternal antibody levels in new-borns from varicella-vaccinated mothers.)

5.3 Safety

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 [139]. 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. The only vaccine-related systemic adverse reactions reported at a significantly greater rate in MMRV recipients were fever and a measles-like rash [139]. 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 [147]. Chaves et al [148] reviewed the US Vaccine Adverse Event Reporting System data from 1995 to 2005 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 [148].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 [149].

As regards reported HZ cases, laboratory tests demonstrated that they might be associated with vaccine or wild-type varicella virus [150,151], 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 no increase in the frequency of HZ in this population [152]. However the long-term effect of varicella vaccination on the incidence of HZ is unknown at present.

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 [147].

For combined MMRV vaccines, the most salient safety finding after widespread use 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 compared to children vaccinated concomitantly with varicella and MMR vaccine [153] [154] [155]. 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 [154]. Similar observations were reported for a matched cohort study performed in Germany [155]. 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 and Germany.

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 febrile seizures after a first dose of a combined MMRV vaccine 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 [156-158].

Several observational studies have reported frequency of BV in vaccinated individuals and results vary significantly between studies and years of observation [159-165]. This may be related to differences in the studies regarding vaccination coverage, 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 varicella vaccination in children is 85% effective in preventing all varicella (median; range 44–100% in post-licensure studies) [166], therefore approximately 15% of vaccinated individuals may develop BV if exposed to VZV.

BV is caused by primary (failure to seroconvert or to mount a protective immune response despite seroconversion) or secondary (waning immunity) vaccine failure. However, no conclusive evidence is available for the different risk factors of vaccine failure, apart from in the case of receiving varicella vaccine within 28 days of MMR vaccine.

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) [122]. Moreover, in a study in Germany [167], 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 difference in BV rate was found between subjects who had received MMR+V concomitantly or after a six-week interval [132] .

Younger age at vaccination (≤14-18 months) may be a risk factor for vaccine failure [168], but the evidence was not consistent and several articles found no association between BV and age at vaccination [157,167,169-175].

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 [132,157,158,171,172,175-177]. However a few studies [173,175,178-180] 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 [122,180,181].

A study by Bonanni et al. in 2013 showed no consistent trend between BV rate and time since vaccination [182]. Another recent study by Baxter et al. in 2013 [183] 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 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.

Conclusions

- BV is usually mild.
- No conclusive evidence is available for the different risk factors of vaccine failure; however type of vaccine, number of doses, age at vaccination and time since immunisation could have an influence.
- Recent studies show no consistent trend between BV rate and time since vaccination.
- Recent studies, in populations mainly vaccinated with one dose, show a varicella vaccine effectiveness of 90% after 14 years.

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 [167].[167] The description of outbreaks in vaccinated populations provides an opportunity to study vaccine effectiveness, risk factors for BV and vaccination coverage.

Most of the outbreaks in vaccinated populations, described to date in USA [172,173,178,184-186], Germany [167], Spain [175], Israel [187] and Uruguay [188] 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 individual vaccines.

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. [185] 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.[189] 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 (85–90%) and sustained vaccine coverage can be achieved [190]. 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, such as ProQuad ® [191] and vaccines authorised nationally such as Priorix Tetra ®, Varilrix ®, Varivax ® and associated names [192].

Monovalent vaccines are available in 28 countries and combined vaccines (MMRV) in 15 countries (AT, BE, CY, CZ, EE, DE, HU, IT, LV, LU, MT, NL, PL, SK, SI) [193].

In October 2012, there were various types of recommendation regarding varicella vaccination in 22 out of 29 EU/EEA countries [193]. In seven countries there is no specific recommendation for varicella vaccination (BG, CZ, HU, PT, RO, SK, SE).

In five countries (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.

Seventeen 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) [193].

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

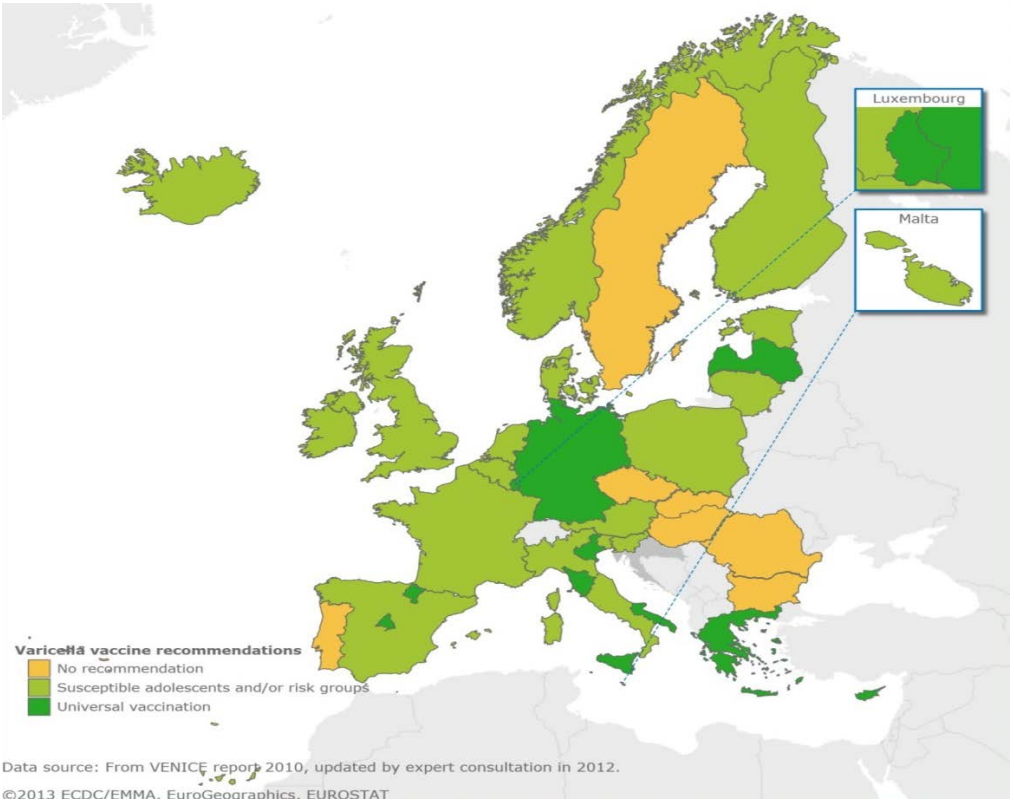

Table 1. Year of introduction, number of doses and age of varicella vaccination in EU and EEA/EFTA countries with childhood universal vaccination, 2012

	Year of introduction	First dose	Second dose
Germany	2004[1]	11-14m	15-23m
Latvia	2008	12-15m	-
Greece	2006	12-15m	4-6y
Cyprus	2010	13-18m	4-6y
Luxemburg	2010	12m	15-23m
Italy			
Sicily	2003	2y	-
Veneto	2005	15m	3y
Puglia	2010		
Toscana	2010		
Spain			
Madrid[2]	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] Programme withdrawn in 2013.

Conclusions

- Varicella vaccine recommendations in the EU/EEA are heterogeneous: only five countries universally recommend varicella vaccination for children at national level and two countries at regional level.
- Seventeen 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 [194]. Additionally, two doses were recommended for unvaccinated adolescents aged 9–17 years with no previous history of varicella [194]. 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) [106,159,195], by outbreak investigation (2008/09) [167] 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) [167]. 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. [196] 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 [195].

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 [197] [196].

Vaccine effectiveness was assessed for outbreaks in day-care settings [162] as well as in a time series analysis using sentinel and coverage data [191], and a recent age and practice-matched case-control study [193].

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 [159]. 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 [198]. Meanwhile, in the AGV-sentinel varicella complications decreased by 81% [104].

Similar results were yielded by the regional surveillance in Bavaria: Incidence estimates of varicella cases in outpatient-children from the area of Munich decreased by over 77%, (from 78.1 to 19.2 per 1 000 children) from October 2006 to September 2011 [189].

Between 2005 and 2009, in the Munich area the incidence of varicella hospitalisations in children under 17 years 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 [189]. 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%) [195], and Streng et al., poster at ESPID Conference 2011).

As regards HZ, a steady number of HZ cases per reporting sentinel physician was observed during the period of the AGV sentinel surveillance [159]. 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 [159]. Coverage as estimated by billing data increased over time, indicating a growing acceptance of varicella vaccination in parents and doctors [195,197,199] [196]. Coverage differed by age and region [167,199]. 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 [159,199]. According to billing data, coverage was estimated to be about 78% at 24 months in 2008 [200]. 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 [198]. 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. [201] 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% [159].

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 [196].

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 [167].

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% [200].

A recent case-control study of paediatric practices in Germany by Liese et al. 2013 [202] 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 [167], 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, varicella vaccine is universally recommended for paediatric vaccination. However, so far only four regions have implemented such a programme. No data are available for Puglia and Tuscany, where the programme was only started in 2010 [75].

In Sicily, the vaccine has been universally administered, since 2003, in the second year of life, 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 [160].

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 on the incidence of varicella infections [64].

Conclusions

- Rapid reduction of the incidence of varicella in Sicily and reduction of both incidence and hospitalisation rate in Veneto.
- No data available relating to the impact on zoster as yet.

Spain

In Spain there is selective vaccination of all susceptible teenagers at 10–13 years (age depends on the autonomous community).

Additionally, in two autonomous communities (Madrid and Navarre) and in the autonomous cities of Ceuta and Melilla, universal childhood vaccination programmes are in place (see schedules in Table 1). Experiences presented here are from Madrid and Navarre as epidemiological data is not available for Ceuta and Melilla.

In Madrid [203], 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%) [203]. 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 2013.

In Navarre [204], 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 those considered susceptible born between 1990 and 1996 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 [204].

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).

Latvia

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

Greece

Universal coverage introduced in 2006 with two doses, the first between 12 and 15months and the second between four and six years.

Luxembourg

Since November 2010, the varicella vaccination is only recommended (no universal coverage). In Luxemburg two doses are recommended, the first at 12 months and the second between 15 and 23 months.

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 developed in 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 [205]. 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 [206]. 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) [207].

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 [205]. 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 [208,209]. 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 [164]. 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 [185]. 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 [206]. 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 [210]. 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 [211].

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 4-12 times lower risk of contracting HZ than unvaccinated children [212,213]. Overall, HZ incidence in the United States is rising in persons of all ages, however increases in HZ began before the varicella vaccine was licenced and therefore do not appear to be solely attributable to varicella vaccination [214]. Trends in HZ incidence are challenging to interpret, given that the risk factors for HZ, other than age and immunosuppression, are poorly understood.

Given that single dose varicella vaccination in children is estimated to be 85% effective (median; range 44–100% in post-licensure studies) [166], 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 [162]. 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 [215].

The decline in varicella incidence reached its nadir in 2002, after which incidence remained stable [164,216]. 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 [149]. 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 [216]. 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 [217-219]. 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 [189,217].

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

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. [220].

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 [82,221-225] [226] . However, a 'post-honeymoon' epidemic is likely to follow, before a new, lower equilibrium level of varicella is reached [82,225].

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 [227], and they are more frequent if a one-dose strategy is used [228]. 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 [221].

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 [82,221]. 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 [221,227]. 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 near elimination of varicella [82,220,222,225,228]. Catch-up campaigns would have no effect on varicella incidence after achieving a long-term equilibrium [227].

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% [221,222,224,227-229].

A routine adolescent vaccination strategy would have limited impact on natural varicella, even where coverage is high (e.g. 95%), since most adolescents already have natural immunity [220,230]. However, 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 [221,225,231].

Model results are highly sensitive to assumptions made about age-dependent contact rates [220,221,224,225] and vaccine efficacy [82,220,225,228]. More recent models [221,222,225] have used empirical findings from diary-based surveys of contact patterns [232], meaning that the models reflect varicella seroprevalence data more closely [233]. There is still little evidence relating to long-term vaccine efficacy, particularly for a two-dose strategy [228].

Conclusions

- Results from modelling are country-specific and are highly sensitive to assumptions about age-specific contact rates 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 [82,221,222,224,225,227] [226]. These models suggest that routine infant varicella vaccination will cause zoster incidence to increase in the medium term. However, in the 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 [222,225,227,228,234].

Introducing HZ vaccination for older adults may mitigate the effect of infant varicella vaccination on HZ incidence, but only to a very small extent [228,231].

ECDC funded a multi-country model [1,2] 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 [3]. 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 increases of HZ in the context of mass varicella vaccination.

Conclusions

- Most models that assume the exogenous boosting theory predict that universal varicella vaccination will cause HZ to increase in the medium term (up to 35–75 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 [235-237]. 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 [234,236]. A few models also took into account potential waning of vaccine protection.

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 [235-237]. 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 worthwhile. 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 [230,238,239] [226]. 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 [230]. Vaccination of susceptible pregnant or postpartum women following anamnestic and serological screening appeared to be cost saving [240,241], although vaccinating against varicella in pregnancy is currently contraindicated. Vaccination programmes targeted at healthcare workers may be cost-effective from an employer's perspective [236]. Vaccination of children prior to organ transplant was highly cost-effective from both hospital and societal perspectives [242,243]. 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 [244,245].

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.
- 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. For example, the seroprevalence was marginally lower among children in southern and eastern European countries than in northern and western European countries. This has been partially attributed to the varying use of day-care and pre-school facilities, different social contacts or to the contrast in climates (i.e. Mediterranean versus temperate).

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 systematic review, 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.

It should be up to individual countries to understand their own baseline hospitalisation rates so that they can monitor them after the introduction of varicella vaccine and understand 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 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. A recent study by Bonanni et al. [182] suggests that a short interval between two doses might be preferable for reducing BV.

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 febrile seizure after a first dose of a combined MMRV vaccine at age 12–23 months.

Febrile seizures are not uncommon in young children and generally have an excellent prognosis, although some require hospitalisation and they are distressing to parents [246]. A second dose of MMRV is less likely to cause fever and 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-)[246]. However, practices in the USA [247] and in Germany recommend separate application of MMR and varicella vaccine for the first dose.

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 (85–90%) can be achieved [190]. 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

Varicella vaccine effectiveness is not 100%, so BV cases do occur, mainly after one-dose vaccination. In studies that have compared the clinical characteristics of varicella among vaccinated and unvaccinated subjects, vaccinated cases had fewer skin lesions, the rash for a shorter period of time, less likelihood of developing fever and fewer complications.

No conclusive evidence is available for the different risk factors of vaccine failure; however type of vaccine, number of doses, age at vaccination and time since immunisation could have an influence.

A recent study from Bonanni [182] has showed no consistent trend between BV rate and time since vaccination, suggesting that a short interval between two doses might be preferable to reduce BV.

Another recent study [183] showed a lasting effectiveness of the vaccine which did not wane over a 14-year period. As has been pointed out before [248], post marketing studies on varicella involving a one-dose schedule or a low vaccine coverage could be confounded through periodic exogenous exposures, prevalent before a two-dose regimen is implemented and/or high coverage reached. This issue has also been raised by modelling studies which predict that BV incidence may be higher than reported in clinical trials, since in a population setting with high coverage, there is less opportunity for vaccine-induced protection to be boosted by natural exposure to varicella.

Experience of varicella vaccination in outbreaks has shown that varicella vaccination strategies have been reported to decrease the number, size and duration of varicella outbreaks and that reductions were even higher with a two-dose schedule.

One-dose varicella vaccination strategies have reported an increase in the median age of patients during outbreaks (from six to nine years), however, there was no data available for two-dose schedule strategies.

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 Santé 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[2].

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[3]. 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.

Seventeen 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.

To date, there is no clear evidence of the 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, are poorly understood. Monitoring the impact of varicella vaccine on HZ remains a priority.

It is possible to attain vaccination coverage above 80%, as recommended by WHO [190]. High vaccination coverage is important because the complication rate for varicella increase with age.

The expected acceptance of varicella vaccinations by parents and physicians and affordability/reimbursement of the vaccine in order to achieve high coverage may be country-specific and this will need to be explored before implementing vaccination.

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

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

Insights from modelling

Results from mathematical modelling are country-specific and highly sensitive to assumptions about age contact rates and vaccine efficacy.

Estimates of the number of BV cases expected, long-term duration of vaccine protection, vaccine coverage level and the impact on zoster come mostly from modelling studies.

These models predict a rapid and sharp decrease in the number of varicella cases in the first decade following varicella vaccine implementation, as has been seen in surveillance.

Overall, two-dose strategies were found to give better results for reducing varicella incidence and decreasing the number of outbreaks. At low coverage levels (<50%) and/or if one-dose strategies are adopted, epidemics consisting of both natural and BV may reoccur at regular intervals. Additionally, if coverage is <80%, some models predict a shift in the average age of infection, with an absolute increase in adult cases.

Models based on the hypothesis that contact with VZV boosts HZ immunity predict an increase in HZ in the medium term (30–75 years) followed by a decrease. The predicted increase in HZ incidence was slightly higher for all two-dose strategies than one-dose strategies, and adding HZ vaccination may mitigate this increase to a very small extent.

One model suggests that the short/medium-term impact of varicella vaccination on HZ is country-specific and therefore an increase in HZ can only be expected to occur in countries where HZ incidence is low due to a higher boosting force.

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 exogeneous boosting of immunity to HZ, the perspective of those evaluating (healthcare provider or society) and the time horizon applied.

Studies examining varicella outcomes alone mainly suggest that infant varicella vaccination (12–24 months) with one or two doses may be cost-effective from the perspective of the healthcare provider. From a societal perspective, infant vaccination is likely to be cost-saving, even when the detrimental effect of zoster boosting is taken into account. The majority of cost savings occur as a result of preventing indirect societal costs (time off from work due to sickness or to care for children with varicella).

If economic evaluations incorporate the effect of boosting immunity to zoster, the increase in morbidity and healthcare costs due to zoster outweigh the decrease in morbidity resulting from varicella in the medium term. However, in the longer 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 increases in HZ to date. In the US this has been demonstrated for more than 15 years now.

Health economic models suggest that introduction of the vaccine may be cost-effective if there is no associated increase in HZ incidence, and may even be cost- saving if indirect societal costs are included. If the HZ boosting hypothesis is assumed, then models predict a net increase in morbidity and healthcare costs for up to 50 years in some countries, after which net morbidity and healthcare costs will decrease.

However, better post-vaccination surveillance and epidemiological research is needed to fill the knowledge gaps, as they are likely to influence the decision regarding the implementation of the vaccine. These gaps include duration of vaccine-induced immunity, need for further doses, impact of vaccination coverage, risk of increasing complications due to varicella following shifts in the mean age of infection following vaccine introduction, risk of complication in adult BV cases occurring several decades after vaccination and potential increases in HZ incidence following varicella vaccination.

Additionally, it is important to consider the expected acceptance of varicella vaccinations by parents and physicians and the affordability/reimbursement of the vaccine in order to reach high coverage.

There are differences in incidence and force of infection in the EU/EEA. These differences should also be taken into account when assessing recommendations for varicella vaccination at country level as they will have important implications for the design and implementation of a VZV vaccination programme.

Better surveillance systems along with a sero-based study on varicella exposure, quantitative IgG response and zoster incidence would give clarity to some of these uncertainties.

While waiting for more evidence on several aspects of varicella vaccination, countries should assess their individual epidemiological and socioeconomic situation, as well as the capacity to achieve high vaccination coverage with the vaccine.

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Annexes

New evidence on 'burden of varicella in Europe'

Search in PubMed

From 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 <22 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

From 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.

Bozzola E, Tozzi AE, Bozzola M, Krzysztofiak A, Valentini D, Grandin A, Villani A. Neurological complications of varicella in childhood: Case series and a systematic review of the literature. Vaccine. 2012 Aug 24;30(39):5785-90. Epub 2012 Jun 5. PubMed PMID: 22683522.

Goldman GS, King PG. Review of the United States universal varicella vaccination program: Herpes zoster incidence rates, cost-effectiveness, and vaccine efficacy based primarily on the Antelope Valley Varicella Active Surveillance Project data. Vaccine. 2012 Jun 1. [Epub ahead of print] PubMed PMID: 22659447.

Marin M, Zhang JX, Seward JF. Near elimination of varicella deaths in the US after implementation of the vaccination program. Pediatrics. 2011 Aug;128(2):214-20. Epub 2011 Jul 25. PubMed PMID: 21788222.

Manikkavasagan G, Dezateux C, Wade A, Bedford H. The epidemiology of chickenpox in UK 5-year olds: an analysis to inform vaccine policy. Vaccine. 2010 Nov 10;28(48):7699-705. Epub 2010 Sep 23. PubMed PMID: 20869468.

Pozza F, Piovesan C, Russo F, Bella A, Pezzotti P, Emberti Gialloreti L. Impact of universal vaccination on the epidemiology of varicella in Veneto, Italy. Vaccine. 2011 Nov 28;29(51):9480-7. Epub 2011 Oct 19.

No extra references were found in Embase