Should Universal Chickenpox Vaccination Be Included in Routine Vaccination? A Critical Analysis of the Literature

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Abstract
Background
Varicella is a well-known infectious disease caused by the varicella zoster virus. It usually is a self-limiting disease. However, severe complications requiring hospitalisation, and long-term sequelae can occur.

Methods
A critical analysis of the literature was performed to analyse arguments pro and contra universal vaccination.

Results
The currently licensed vaccines are highly effective in preventing varicella infection and the possible severe complications. They are safe with generally mild adverse effects. Cost-effectiveness studies show a benefit for the society. However, high vaccine coverage rates are needed to prevent the shift in varicella cases to older age groups. This can be achieved when administered in combination with the already established measles mumps rubella (MMR) vaccination at the age of 12 months.

Conclusion
Universal varicella vaccination is recommended if high coverage rates can be achieved.

Introduction

Varicella is caused by the varicella zoster virus (VZV), a member of the *Alphaherpesvirinae* subfamily (1, 2). VZV is characterised by its ability to settle in the dorsal root ganglia, causing lifelong latent infection (1, 2). Varicella is highly contagious, with a reproduction number (R0) of between 3.3 and 16.9, and is primarily transmitted via airborne infectious respiratory particles and by direct contact with the vesicular rash associated with varicella or herpes zoster (1, 2). The clinical picture is well known to paediatricians. The different clinical phases are summarised in Table 1. The diagnosis is clinical, but PCR can confirm acute cases. Serological tests are useful to identify seronegative individuals and can differentiate between primary infection and reactivation (1). Varicella primarily affects young children, with most having been infected by the age of 10 (1-3). Between 90 and 95% of individuals will have been infected by adulthood (2). The exact disease burden of varicella is difficult to assess as it is not a notifiable disease in many countries (3). However, it has been estimated that the number of cases annually is roughly proportional to the size of a country's birth cohort. Between 2021 and 2024, the average number of births in Belgium was 108,696 per year (4).

Complications occur in 2-6% of the cases (3, 5). It is important to note that the majority of these occur in healthy children with no underlying conditions (6). The most common complication is a secondary bacterial infection (1-3). Necrotising fasciitis is a rare, but life-threatening complication (7). Other complications include laryngitis, pneumonitis, thrombocytopenia, hepatitis, deep vein thrombosis, stroke and neurological problems such as cerebellar ataxia, encephalitis, Guillain Barré syndrome, meningitis, and transverse myelitis (1, 5, 8-10). Complications often result in hospitalisation (8). Between 2010 and 2019, an average of 767 hospital admissions per year were recorded in Belgium (11). The highest hospitalisation rates were seen in children 0-12 months (3). Long-term sequelae such as severe scarring, ataxia and epilepsy are present in 0.4–10.1% of children hospitalised for varicella (3, 5). Varicella is responsible for around 4,200 deaths worldwide each year (12). The case fatality rate for varicella in high-income countries has been estimated at 2–4 per 100,000 cases (13). These figures challenge the common perception that varicella is always a mild disease and not a priority for policymakers.

If a pregnant woman contracts varicella in the first or second trimester, her foetus may develop congenital varicella syndrome. Defects and scarring of the skin, abnormalities of the limbs, brain and eyes, and low birth weight, and even foetal death, occur in 0.4–2% of infants born to mothers who became infected with VZV during the first 20 weeks of pregnancy (1, 5, 14). If a woman contracts varicella from five days before to two days after giving birth, her newborn baby may develop severe varicella due to an insufficient transfer of maternal antibodies. The mortality rate in such cases can be as high as 30% (1, 5, 14).

Herpes zoster (shingles) is caused by the reactivation of a latent VZV infection, which typically results in a painful vesicular rash in a single dermatome (1). However, reactivations are most commonly subclinical (1). Pain is caused by acute neuritis (2). Post-herpetic neuralgia develops in around 50% of adults and is often difficult to treat (2, 5). Herpes zoster occurs in 10-20% of people after primary infection with an increasing incidence with age (1).

Treatment for uncomplicated varicella is usually supportive only (1). Early treatment with antiherpetic agents may be considered for children at high risk of complications and is often started in adolescents and adults (1). Immunotherapy with anti-VZV antibodies is an effective alternative for specific patients such as immunocompromised individuals, pregnant women with no evidence of immunity against VZV, and newborns exposed postnatally (1).

TABLE 1: The different phases of VZV infection.

Phase	Pathophysiology	Signs and symptoms
Incubation time (14-21d)	Replication in epithelial cells of tonsils	Signs and symptoms
Prodromal phase	First viraemia	No
Second viraemic phase (14d after infection)	Spread to skin and mucous membranes	Fever, generalised malaise and loss of appetite
		Vesicular rash - Face/trunk → extremities - Vesicles → pustules → crusts - +/- involvement of oral mucosa
Healing phase (1-2w)		All lesions scab

Varicella vaccination

All available varicella vaccines are live, attenuated vaccines. With the exception of South Korea, where the MAS strain is used, all other licensed vaccines are based on the OKA strain. New vaccines are under development, for example in China (15). Takahashi developed the OKA strain in Japan, deriving it from a wild-type strain isolated from the vesicular fluid of a child with varicella (1). In 1974 the vaccine was given to 23 children in a Japanese clinic and successfully prevented varicella transmission from an infected child admitted to the same ward (1). The vaccine is available as a single-antigen vaccine or as a combined measles-mumps-rubella-varicella (MMRV) vaccine. The single antigen vaccine was licensed in several European countries in 1984, the combined antigen vaccine was approved by the US Food and Drug Administration (FDA) in 2005 and by the European Medicines Agency (EMA) in 2006 (16, 17). The vaccine's efficacy and effectiveness have been investigated in various studies.

Vaccine efficacy

Table 2 provides an overview of the cited efficacy studies.

A double-blind, placebo-controlled efficacy trial of a single dose of the single-antigen live-attenuated Oka varicella vaccine was conducted in the USA in 1984. A total of 914 children aged 1-14 who had not previously had varicella were included (18). The vaccine was well tolerated, with none of the vaccinated children contracting varicella during the 9-month follow-up period (18). However this short follow-up period did not allow definitive conclusions to be drawn. The same authors published the results of a 2-year efficacy and a 7-year follow-up study a few years later (19). They concluded that the overall vaccine efficacy was 98% after 2 years and 95% after 7 years (19). The breakthrough cases had considerably milder disease than natural varicella (19).

In 2005, a randomised controlled trial involving healthy children aged between 12 and 22 months was conducted in 10 European countries. Of the children involved, 2,263 received one dose of the single-antigen varicella vaccine together with the second dose of MMR (MMR+V); 2,279 received two doses of the combined-antigen vaccine (MMRV); and 743 received two doses of MMR (20). After three years, an evaluation of efficacy showed that a single-antigen dose was 64.5% effective against all varicella and 90.7% effective against moderately severe to severe varicella. For the two-dose combined antigen vaccine, the efficacy rates were 94.9% and 99.5%, respectively. A re-evaluation after ten years showed an efficacy of 67.2% against all varicella and 89.5% against moderately severe to severe varicella for a single-antigen dose. For the two-dose combined antigen vaccine, the efficacy against all varicella was 95.4%, and against moderately severe to severe varicella, 99.1% (21). It is important to note that combining the varicella antigen with the MMR vaccine does not reduce the MMR efficacy (22, 23).

TABLE 2: Overview of efficacy studies.

Authors	Study type	Vaccine	Numbers of children	Study period	Efficacy
Single dose studies					
Weibel,RE et al., 1984 (15)	Double blind placebo controlled	Single-antigen 1 dose	914	9 months	(100%)
Kuter B et al., 1991 (16)				2 years 7 years	98% 95 %
Prymula, R et al., 2014 (17)	RCT	Single-antigen added to MMR (MMR+V) 2 doses	2263	3 years	64.5
Povey, M et al., 2019 (18)				10 years	67.2%
Two dose studies					
Prymula, R et al.,2014 (17)	RCT	Combined antigen (MMRV) 2 doses	2279	3 years	94.9%
Povey, M et al., 2019 (18)				10 years	95.4%

TABLE 3: Adverse effects of the varicella vaccine.

Frequency	Adverse effect	Sources
Very Common ≥ 10%	Soreness Redness at injection site within 3 days	CDC (21); Product Monograph
Common ≥ 1% and < 10%	Fever ≥ 38°C Swelling at injection site Irritability Disturbed sleep	CDC (21); Product Monograph; Woodward et al. (35)
Uncommon ≥ 0.1% and < 1%	Upper respiratory infection Headache Nausea, vomiting Varicella like rash Myalgia	Leung et al (14).; Product Monograph
Very rare ≥ 0.01% and < 0.1%	Febrile convulsions Pneumonia Hepatitis Meningitis Disseminated vaccine strain infection Anaphylaxis	Woodward et al. (35); Casabona et al.(56); CDC (21); Committee to Review Adverse Effects of Vaccines (36)

Vaccine real world effectiveness

Although varicella vaccination is licensed in many countries, it is included in immunisation programmes in only some of them. The United States of America (USA) was the first country to implement a national varicella vaccination programme in 1995, initially with a single dose schedule and changing to a two-dose schedule in 2006 (12–15 months and 4–6 years), achieving high coverage (93.3% for the first dose in 2021–2023, 92.1% for the second in 2024–2025) (3, 24-26). A few years after implementation Vázquez et al. conducted a matched case-control study to evaluate the effectiveness of the varicella vaccine (27). They calculated the vaccine effectiveness to be 87% against all varicella and 97% against moderately severe and severe varicella. The number of varicella cases reported annually decreased from four million before 1995 to fewer than 15,000 in 2024 (25). The annual varicella-related hospitalisation rate in the USA decreased from 0.5 hospitalisations per 10,000 population from the pre-vaccination era to 0.26 per 10,000 population by 1999, and halved again to 0.13 per 10,000 by 2001 (28). It is currently estimated that 10,500 to 13,500 hospitalisations are prevented annually (25). Hospitalisation associated costs more than halved as well (28). Furthermore, an 88% decline in the annual average mortality rate for varicella was observed from 1990-1994 to 2005-2007 (29). It is estimated that 100 to 150 varicella-related death are prevented annually (25).

Germany introduced universal vaccination with a single dose of the varicella vaccine to its immunisation schedule in 2004. In 2009, this was changed to a two-dose schedule (30). The vaccine is administered together with the measles, mumps, rubella (MMR+V) vaccine or as a tetravalent vaccine (MMRV) (30, 31). The vaccine effectiveness was 86.6% after one dose and 97.3% after two doses. Hospitalisations decreased by 65%. Even herd immunity effects were noted in paediatric oncology patients, who are not eligible for vaccination (30). No evidence of a shift towards older age groups was observed (32). Nor was the incidence of herpes zoster affected (30).

Italy introduced universal varicella vaccination (UVV) in several regions between 2003 and 2011. For example, UVV was introduced in Tuscany in 2008. Over the 10-year period from 2010 to 2019, the vaccine effectiveness after one dose was 84.8%, and after two doses 95.7%. The effectiveness in preventing varicella-related hospitalisations reached 98.5% (33). Moreover, a decrease in varicella incidence was noted, from 164 cases per 100,000 in 2006 to 101 cases per 100,000 in 2009 ($p < 0.01$), across the whole country, following the introduction of a single dose of the vaccine in just a few regions (27). In 2017, Italy implemented a national, mandatory (and reimbursed) UVV programme with a two-dose schedule (30, 34). A coverage of 90% was achieved in 2019. The incidence rate of varicella decreased from 49.8 per 1,000 person-years in 2017 to 3.2 per 1,000 person-years in 2022 (34). A notable decrease in varicella-related complications was also observed (30).

A 2021 Cochrane review examined the effectiveness of the MMR+V or MMRV vaccine in children aged up to 15 years. The effectiveness against all forms of varicella was 95% in children aged 11 to 22 months after two doses, over a follow-up period of 10 years (22).

All studies and data confirm that a two-dose vaccine schedule is more efficacious and effective than a one-dose schedule. Although the manufacturers recommend a minimum interval of four weeks between doses, various countries use longer intervals (up to five or six years). This does not appear to have a significant impact on the increase in antibody titres (24, 30, 35, 36).

Post-exposure prophylaxis

Post-exposure vaccination reduces infection rates and the severity of cases in over 90% of susceptible individuals when administered within three days of exposure. The sooner the vaccine is administered, the more effective it is, with an effectiveness rate of up to 95% being achieved. In varicella outbreak settings, where exposure risk may persist for weeks, a second dose may be indicated (8, 37, 38).

Possible adverse effects of varicella vaccination

The live, attenuated OKA strain of varicella-zoster virus (VZV) is a safe vaccine. In a 22-year post-marketing safety review, only 0.8 reports of serious adverse events were recorded per 1 million doses (39). However, like any other vaccine, the varicella vaccine can have adverse effects. These are summarised in Table 3. According to the Committee to Review Adverse Effects of Vaccines, there was insufficient evidence to establish a causal relationship between vaccination and neurological symptoms such as encephalopathy, seizures, cerebellar ataxia, acute disseminated encephalomyelitis, transverse myelitis, and Guillain–Barré syndrome (40). In 2010, Klein et al. reported a higher incidence of febrile convulsions following the first dose of the MMRV vaccine compared to the MMR+V vaccine, respectively 7–9 cases per 10,000 children versus 3–4 cases per 10,000 children (41). This equates to one additional case of febrile convulsions per 2,300 doses of the MMRV vaccine administered (37). However, this only applies to the first dose, not the second (42).

Breakthrough varicella

Breakthrough varicella is defined as varicella caused by the wild-type VZV, occurring at least 42 days after receiving at least one dose of the varicella vaccine (15). Breakthrough varicella is most frequent after a single dose of the vaccine, due to either primary vaccine failure or waning immunity, and is generally much milder than natural varicella. However, severe breakthrough cases are rare. These include severe infections, such as pneumonia or sepsis, neurological complications, and any hospitalisation or

death (15). Adding a second dose to the vaccination schedule reduces the incidence and severity of breakthrough cases by six to nine times (20, 30).

Possible concerns about introducing universal a varicella zoster vaccination programme

Notwithstanding the occurrence of severe cases of varicella, complications and fatalities, and despite the proven effectiveness and safety of the vaccine, universal vaccination against chickenpox has not yet been implemented in all countries (3). Reasons for not implementing include concerns about the duration of protection, the possibility that vaccination could cause varicella to shift to older age groups, mathematical models predicting possible increases in herpes zoster incidence due to the elimination of exogenous boosting, and questions about cost-effectiveness given that varicella is perceived as a mild disease (3).

Duration of protection

The duration of protection following varicella vaccination is currently unknown. Although studies had demonstrated no waning of antibodies over nine to 14 years, the most interesting study is from Italy and was published by Bianchi et al. in 2021 (43-45). A seroprevalence study was conducted among 182 adult medical students who had received two doses of the varicella vaccine in childhood. 34.1% of these students had no protective antibody titres. Antibodies wane over time. An antibody survival model was used to calculate that half of the fully vaccinated population will have lost circulating antibodies after nine years. However, a booster dose in the seronegative group was 100% effective. It should be noted that the cellular-mediated immunity was not examined directly.

Varicella shift to older people

A major concern is that by vaccinating young children, the occurrence of varicella will shift to older age groups (46). The risk of varicella-related complications and death is higher in adults (5, 47). Some authors fear that severe cases of varicella could offset the benefits of the vaccine in children (47). However, following the introduction of a universal varicella vaccination programme in Germany and Italy, no increase in incidence was observed in older age groups (30). In fact, an overall decrease in incidence was observed due to herd immunity (30). This can only be achieved if an immediate and sustained high vaccination coverage rate is achieved (46). The WHO recommends a two-dose schedule and a coverage rate of more than 80% (48). Compliance can be enhanced by concomitant administration with the MMR vaccine, either as an add-on or as the tetravalent vaccine, as the majority of European countries with available data achieve MMR vaccine rates of 85% or more (5, 46). Catch-up campaigns can help if initial coverage is low (47).

Increased herpes zoster incidence

In 1965, Hope-Simpson published his research on herpes zoster, proposing the hypothesis that it resulted from the reactivation of the VZV virus following a decline in immunity. This could be counterbalanced by boosting immunity, 'endogenously' through subclinical reactivation of latent VZV, or 'exogenously' through exposure to individuals with varicella (49, 50). By vaccinating large cohorts of people this boosting effect may disappear, potentially causing more herpes zoster infections in the elderly (51). Mathematical modelling based on the 'exogenous boosting hypothesis' predicted a major herpes zoster epidemic in adults following the introduction of varicella vaccination (52). This theoretical risk has been occupying the minds of many policymakers ever since. Many studies have been published on the 'exogenous boosting hypothesis', yielding a variety of results. A large self-controlled case series was conducted in the United Kingdom to assess the protective effect of household exposure to a child with varicella on the incidence rate of herpes zoster in adults (53). The results, published in early 2020, confirmed the protective effect of exposure to varicella, albeit only at 30% over 20 years (53). This was confirmed in a study by Ogunjimi et al. on boosting in grandparents exposed to varicella, which showed that boosting occurred in only 16-25% and lasted for less than one year (54). These data suggest that the role of exogenous boosting is more limited than previously thought and used in several mathematical models (53). A 2022 study by Leung et al. found that there had been no increase in the incidence of herpes zoster in the USA, the country with the longest-running UVV programme, during the period from 1998 to 2019 (55).

Van Hoek et al. used mathematical models to look at the cost-effectiveness of introducing universal varicella vaccination for children alongside the available zoster vaccine for the elderly. They concluded this approach could be cost-effective, provided that the zoster vaccination programme is terminated once the vaccinated childhood cohort has reached adulthood (51). An Italian analysis came to the same conclusion (52). In the United Kingdom Finn also proposes moving beyond theoretical discussions about the role of exogenous boosting and finding an explanation for the rise in herpes zoster incidence, and instead looking at the zoster vaccine as a solution to this possible problem (56).

Cost effectiveness

A recent study by Rodrigues et al. examined health-related quality of life (HRQoL) parameters, such as Quality Adjusted Life Years (QALYs), in both ambulatory and hospitalised children, as well as in carers of children with varicella in Portuguese public hospitals between 2019 and 2020 (3). This prospective study concluded that a single episode of varicella that does not require hospitalisation has a relatively small impact on HRQoL. However, admitted cases had a very high impact on HRQoL, on the patients and their families (3). The study demonstrates that varicella infection, with its possible complications has a significant impact on public health, resulting in healthcare costs and loss of work productivity (3).

An Italian transmission model estimated that if a vaccine coverage of 90% was reached, a saving of €1.20 from health system perspective and of €3.50 from societal perspective would be gained for every €1 invested in vaccination (30). In both Germany and Italy, the costs of varicella-related hospitalisation declined by up to 90% within a few years of the implementation universal varicella vaccination programmes (30). In 2003, a Belgian team claimed the cost of implementing a universal varicella vaccination programme would exceed the cost of treating varicella (46). They argued that, from a societal viewpoint, universal infant vaccination is cost-effective because of averted unproductive days for parents, but not from the healthcare payer's viewpoint when considering the price of the vaccine and the costs of implementing the programme (46). From this perspective, vaccinating adolescents and adults is more cost-effective (5, 46). However, this would not reduce overall viral transmission (5). Nevertheless, in 2010, the Belgian Healthcare Knowledge Centre concluded that, if the exogenous boosting theory were not true, universal varicella vaccination with a two-dose schedule would probably be cost-effective at the vaccine price of that moment (57).

Factors to consider when implementing a UVV programme

The World Health Organization recommends varicella vaccination "for the prevention of varicella in populations where it is an

important public health problem" (58). This vague and somewhat disappointing WHO recommendation is understandable because, for policymakers, the significance of concerns listed above in deciding about the implementation of a UVV, is influenced by socio-economic, demographic, cultural and ethnic factors. These include the organisation of the healthcare system, the capacity of UVV funding, the age distribution of the population, demographic disparities, immigration, vaccine hesitancy, and the decline of public trust in institutions and politicians. Currently, as described below, 16 of the 27 countries in the European Union have adopted a UVV programme.

Countries wishing to launch a UVV programme must first establish a robust surveillance system to monitor its effects. It is recommended that this surveillance is made mandatory (6, 59). The survey should include vaccine coverage, effectiveness, age specific incidence of varicella and herpes zoster cases, occurrence of adverse events and disease needing hospitalisation. This will require adapting the existing surveillance systems and the cooperation of all clinicians to report cases. The possibility of self-reporting varicella cases can be explored (55).

A review article published in Vaccine in 2016 identified five determinants of vaccine uptake, known as the 5A's. These are Access, Affordability, Awareness, Acceptance and Activation (60). These determinants are important for the successful implementation of a UVV programme, with the aim being to reach a coverage rate of ≥ 80%.

Access is "the ability of individuals to be reached by recommended vaccines" (60). The varicella vaccine can be added to the existing MMR vaccination schedule. To avoid concerns about an additional injection, the combined MMRV vaccine can be used The slightly increased risk of febrile convulsions should be taken into account (30, 61).

Affordability is "the ability of individuals to afford vaccination, in terms of both financial and non-financial costs (e.g. time)" (60). In order to achieve vaccine coverage of more than 80%, the vaccine must be accessible to all. Full government reimbursement is the ideal scenario (60). If the varicella vaccine is added to the existing MMR vaccination programme, time should not be an issue.

Awareness is "the degree to which individuals have knowledge of the need for, and availability of, recommended vaccines and their objective benefits and risks" (60).

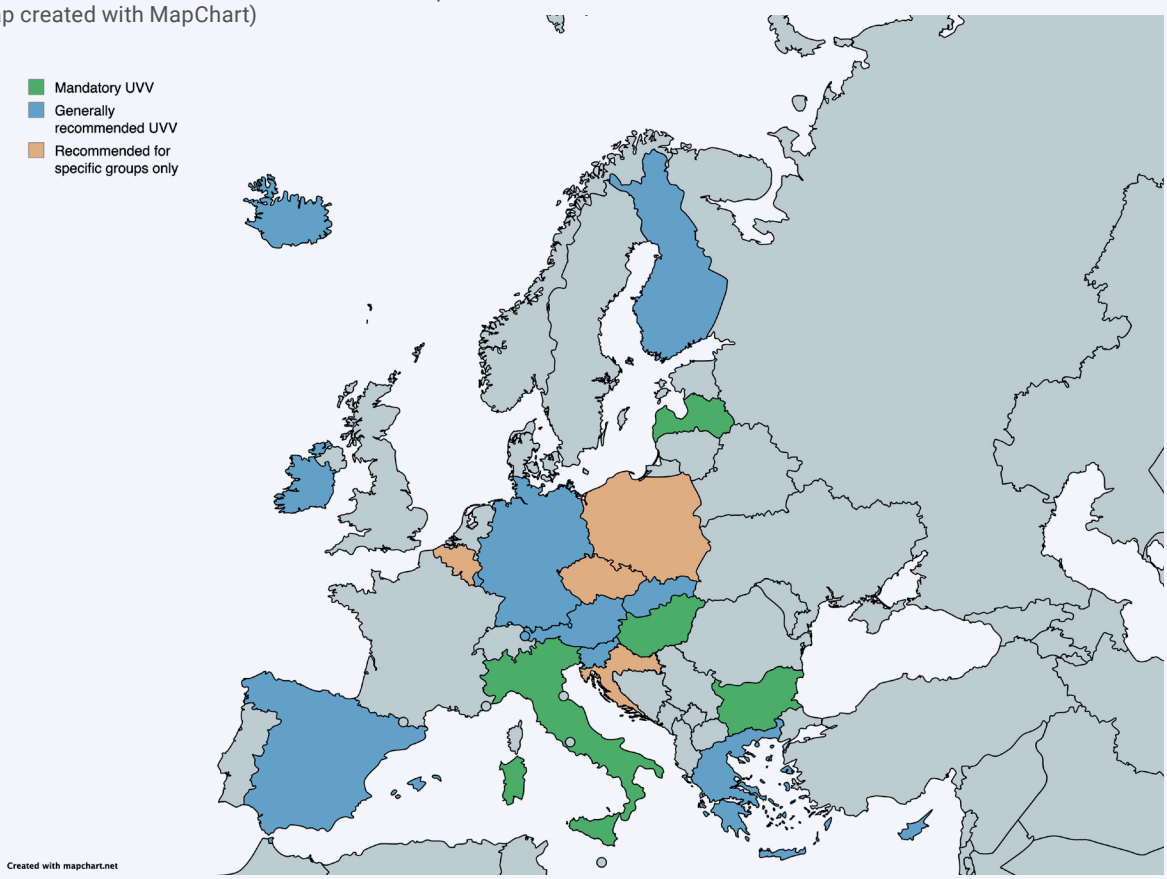
Acceptance is "the degree to which individuals accept, question or refuse vaccination" (60). Examples of acceptance factors include safety concerns, the perceived severity of the disease and, individual health believes (60). A recently published review identified physician recommendation as the strongest factor influencing acceptance of the varicella vaccine (59). Often both parents and physicians view varicella as a mild disease. A 2016 study in the Netherlands proved this to be a major barrier to the implementation of UVV (62). Therefore, it is important to support both parents and physicians with appropriate information before and during the rollout of UVV (59).

Activation "refers to the actions that nudge people who intend to get vaccinated towards vaccine uptake" (60). This includes extra reminders such as leaflets and parent meetings (60). Existing information platforms can be used for this purpose.

Status of varicella vaccination in the European Union countries

Currently, 20 of the 27 European Union countries recommend varicella vaccination as part of their national immunisation programmes (Figure 1). Sixteen countries recommend UVV.

FIGURE 1: Varicella vaccination recommendations in European Union countries in 2026 (map created with MapChart)



Mandatory UVV is in place in four of these countries: Bulgaria, Hungary, Italy and Latvia. It is not mandatory in Austria, Cyprus, Finland, Germany, Greece, Iceland, Ireland, Liechtenstein, Luxembourg, Slovakia, Slovenia and Spain. In four countries, vaccination is recommended for specific groups only: Belgium, Croatia, Chechia and Poland (where it is mandatory) . All countries recommend a two-dose schedule, but at different ages. The ECDC's vaccine scheduler provides an overview (63).

The vaccines currently available in Belgium are two monovalent live-attenuated vaccines called Varilrix and Varivax, and a combined live-attenuated vaccine containing strains of measles, mumps, rubella and varicella called ProQuad. These vaccines are not routinely reimbursed. The Belgian Superior Health Council does not recommend universal vaccination, but only the vaccination of specific groups, including adolescents and young adults with no history of chickenpox; individuals working in the healthcare sector who are not immune; individuals in contact with immunocompromised patients or young children who are not immune; and women who are not immune and are planning to become pregnant (37). However, this approach only protects a few individuals and does not reduce viral transmission in the community (5).

Conclusion

Varicella is a highly contagious infectious disease caused by the varicella zoster virus. Although it is usually self-limiting, severe complications can occur, resulting in hospitalisation and long-term consequences. Reactivation of the latent virus can lead to zoster in adults and the elderly, causing significant morbidity in these age groups. Many studies over the years have shown that the currently available and licensed varicella vaccines are safe and highly effective in preventing infection, severe disease and death. A significant reduction in the number of cases and complications was observed in the countries where UVV has been implemented. The adverse effects are generally mild. Once high vaccine coverage rates have been achieved, herd immunity ensues, protecting those who are not eligible for vaccination. For this reason, we believe that UVV should be recommended.

While most cost-effectiveness studies demonstrate societal benefits due to averted unproductive days for parents, the benefits for healthcare payers can be limited depending on the vaccine's price and the cost of implementing the vaccination programme. If a country wishes to implement universal varicella vaccination, it is crucial that high coverage rates are achieved to prevent varicella cases shifting to older age groups. The combination with the already established MMR programme can increase vaccine uptake. Otherwise, catch-up programmes are recommended. Regarding the unproven theoretical concern of an increased incidence of zoster following the introduction of universal childhood vaccination, countries could consider introducing zoster vaccination at the same time.

Statements

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