Implementing Universal Varicella Vaccination in Europe

The Path Forward

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Abstract: Varicella is a common vaccine-preventable disease that usually presents as a mild disorder but can lead to severe complications. Before the implementation of universal varicella vaccination (UVV) in some European countries, the burden of varicella disease was broadly similar across the region. Despite this, countries adopted heterogeneous varicella vaccination strategies. UVV is currently recommended in 12 European countries. Known barriers to UVV implementation in Europe include (1) a perceived low disease burden and low public health priority; (2) cost-effectiveness and funding availability; (3) concerns related to a shift in varicella disease and incidence of herpes zoster and (4) safety concerns related to measles, mumps, rubella and varicella–associated febrile seizures after the first dose. Countries that implemented UVV experienced decreases in varicella incidence, hospitalizations and complications, showing overall beneficial impact. Alternative strategies targeting susceptible individuals at higher risk of complications have been less effective. This article discusses ways to overcome the barriers to move varicella forward as a truly vaccine preventable disease.

Key Words: varicella, vaccination, disease, risk, burden

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Varicella is a common disease caused by the varicella-zoster virus (VZV). Primary infection usually occurs during childhood leading to clinical varicella or chickenpox. In the absence of varicella vaccination, primary infection with VZV is almost universal, and the highest incidence is observed in children younger than 10 years of age.[1,2] Overall annual varicella incidence rates across European countries before introduction of varicella vaccination were estimated to range between 7.05 (Greece) and 16.1 (the Netherlands) per 100,000 persons in children younger than 5 years of age, corresponding to seroprevalence rates of 35.3% and 80.6%, respectively.[3]

In young children, varicella usually presents as a mild disorder, but severe complications of varicella can occur with the risk of varicella complications increasing with age.[4] Complications include skin and soft-tissue superinfections, as well as neurologic complications and pneumonia. Fatality is estimated at 80 deaths in Europe per year, with neonates and the immunocompromised being at higher risk.[5,6]

After primary VZV infection, the virus becomes latent. Latency is lifelong, and viral activation can occur in older adults leading to herpes zoster (HZ; shingles). Postherpetic neuralgia, a severe and often long-lasting pain, is a common complication.[7] Other neurologic complications include facial palsy, encephalitis and cerebral vasculitis.[8] The risk of zoster increases with age but can occur at any age, particularly in those immunosuppressed.

Live varicella vaccine is well tolerated but contraindicated in persons with immunosuppression and in the first year of life.[9] The vaccine is 80%–85% effective (range, 44%–100%) in prevention of all disease and more than 95% effective in prevention of moderate and severe disease.[10] In a meta-analysis, the vaccine effectiveness of a 2-dose regimen in routine use was 92% [95% confidence interval (CI): 88%–95%].[11] The 2 available varicella vaccines in Europe (Varivax - Merck Sharp & Dohme, Hoddesdon, UK and Varilrix - GSK, Middlesex, UK) consist of the live attenuated Oka vaccine strain[8] and are indicated in 1-dose or 2-dose regimens, dependent on the licensed indication or country-specific recommendations.[12]

For countries where varicella is an important health burden, World Health Organization recommends that if sufficient resources exist to reach and sustain a vaccine coverage level of ≥80%, the introduction of varicella vaccination in the routine childhood immunization program should be considered.[12] In countries with a high proportion of susceptible persons ≥15 years of age, World Health Organization recommends vaccination of adolescents and adults without evidence of varicella immunity.[12]

Based on the experience of a selection of European countries with diverse approaches to varicella control, this opinion paper identifies drivers and barriers to implementation of universal varicella vaccination (UVV) and proposes ways to overcome these barriers by comparing countries with and without UVV.

STATUS OF VARICELLA VACCINATION IN THE EU

Monovalent varicella vaccines are available in all 28 EU member countries and as a measles, mumps, rubella and varicella (MMRV) combination vaccine in 16 countries. As of 2018, 12 countries had UVV recommendations at the national level (Austria, Andorra, Cyprus, Czech Republic, Finland, Germany, Greece, Hungary, Italy, Latvia, Luxembourg and Spain), of which 6 are implemented as publicly funded UVV programs.

In the EU, recommendations for, and implementation of, UVV vary widely. The first European countries to incorporate national-level UVV with a 1-dose schedule were Germany in 2004 and Greece in 2006, 20 years after the Oka strain vaccine was first licensed in 1984 in Japan.[13] UVV recommendations were adjusted to a 2-dose schedule in Germany in 2009 as a result of evidence of continued varicella virus circulation and occurrence of varicella outbreaks.[14] In 2006, an MMRV combination vaccine was first licensed in the United States and subsequently in European countries. In 2011, as a result of the association of MMRV with a small increase in febrile seizures after the first dose, it was recommended in Germany that separate administration of the first dose of MMR and varicella vaccine be used and that MMRV be used for the second dose only.[15,16]

In Italy, progressive regional level introduction of UVV started in 2003 in Sicilia[5] followed by 7 regions (out of 21). By 2012, the Italian regional vaccination programs covered 40% of the total resident population.[5] Varicella vaccination was included in the Italian National Plan for Vaccination in 2005 to 2007 for persons at high risk of complications and susceptible adolescents.[17] Italy's National Plan for Vaccination (2017 to 2019) recommends UVV at the national level following on the experience from existing regional programs.[18] In mid 2017, varicella vaccination had been made compulsory, as well as those against measles, mumps and rubella and those included in the hexavalent vaccine (diphtheria, tetanus, pertussis, poliomyelitis, H influenza type b and hepatitis B).[19]

Spain progressed from a high-risk approach to a UVV in only a few regions and finally to a universal vaccination approach. UVV began in autonomous communities of Madrid, Navarre, Ceuta and Melilla cities, from 12 to 15 months onward (with 1 or 2 doses). In the rest of the Spain, only high-risk patients and rescue vaccination by the age of 12 with 2 doses of the vaccine was reimbursed.[20] Parent followed pediatricians' recommendation to vaccinate their children, and moderate (30%–40%) coverages were achieved, despite the lack of reimbursement. In 2014, as a result of a ministerial decree, Spain restricted monovalent vaccine to hospital use only, depriving the nonhospitalized population access to varicella vaccine in community pharmacies.[21] However, 2 years later, Spain's Ministry of Health announced the inclusion of universal childhood varicella vaccination in the national immunization program beginning in 2016.[22]

In Finland, varicella vaccine was approved for introduction in the national immunization program in 2017, following parliament approval of the public program budget and funding.

Of the countries that have not recommended UVV in the National Immunization Program (Table 1), the United Kingdom and France currently recommend vaccination in selected groups with the aim to prevent transmission and severe forms of varicella. Groups at risk for contracting or transmitting varicella and healthy adolescents and adults without a history of varicella are targeted, and postexposure prophylaxis (PEP) vaccination is used in specific circumstances.[23]

In the United Kingdom, reevaluation of the guidelines was initiated in 2015 by the Joint Committee on Vaccination and Immunisation and is currently ongoing. In France, Souty et al[24] recently suggested that the current varicella vaccine recommendations should be reviewed based on (1) the low vaccination coverage attained by the risk group strategy (estimated at 1% of the population); (2) the limited effectiveness of PEP (62%), in France, when PEP is administered within 3–5 days after varicella exposure in susceptible subjects[24]; (3) the high probability of infection in susceptible adults after exposure through familial contact (32% of 221 adults)[24] and (4) the finding that among the 35% of those 18 years of age with uncertain varicella history, 11% were truly nonimmune. It has been estimated that PEP would only prevent 26% of these cases (13 cases averted per 100,000 adults per year) and 31% of the hospitalizations (0.2 hospitalizations averted per 100,000 adults per year) assuming vaccination acceptance was 70%.[24]

Vaccination Coverage After UVV in Europe

In the countries and regions of Europe with UVV, the vaccination programs have generally reached high coverage rates.

In Spain, vaccination coverage in the 4 regions with UVV in 2011 was 95.0% for dose 1 and 86.1% for dose 2 (in the regions with 2-dose recommendation).[25] Following the restriction to hospital use in 2014, the nationwide vaccination coverage dropped from 45% in 2012 to 2% in 2014. Greece obtained UVV 1-dose coverage above 70% among those 6–7 years of age in 2012, with age-appropriate vaccination being completed by 61% of preschoolers in Athens.[26]

In Germany, vaccination coverage has been increasing since 2006. In 2011/2012, as assessed by a survey of parents based on the records in the child's vaccination booklet, coverage for 2 cities in Bavaria had reached 83% and 68% for the first dose, and 72% and

TABLE 1. Recommendations and Vaccination Programs for UVV in Countries in Europe (as of March 2018)

Country	UVV Recommendation Date	Implementation/Coverage	Regimen*
Austria	2010	National but not implemented (no public funding)	D1 and D2 MMRV between 11 and 23 m (4-wk interval)
Finland	2017	National	D1 MMR+V, 12 m; D2 MMRV, 6 yr
Germany†	2004	National	D1 MMR+V, 11–14 m; D2 MMRV, 15–23 m
Greece†	2006	National	D1 MMR+V, 12–15 m; D2 MMRV, 4–6 yr
Italy†	First regional recommendation (Sicily) in 2002	National	D1 MMR+V, 13/15 m; D2 MMRV, 5–6 yr
Latvia*	2008		D1, 12–18 m
Luxembourg†	2009	National	D1 MMRV, 12 m; D2 MMRV, 15–23 m
Spain†	First regional recommendation (Navarra) in 2006 and then (National) in 2016	National	Navarra: D1 MMR+V, 15 m; D2 MMR+V, 3 yr. National: D1 MMR+V, 15 m; D2 MMRV, 2–4 yr
Cyprus	2010	National	D1, 13–18 m; D2, 4–6 yr

*All countries recommend a 2-dose regimen except Latvia, which recommends a 1-dose regimen.

†UVV is publicly funded.

D1 indicates dose 1; D2, dose 2; MMR+V, measles, mumps and rubella combination vaccine +varicella vaccine given separately.

TABLE 2. Summary of Impact of Varicella Vaccine in Europe

Country	Burden	Herd Immunity	Varicella Age Shift	HZ Incidence	Vaccine Effectiveness
Germany	All cases, >50% reduction; hospitalization, >70%	Indirect protection of <1-yr-old unvaccinated	Not observed	Increasing burden, secular trend?	All 86% dose one; 94% 2 doses
Italy			Secular trends not conclusive	No evidence	All 98% dose one; severe 99% (dose 1)
Greece	Reduction of all cases; reduction of hospitalization and complications		Not observed (small cluster in 2012)	No increased risk in children	
Spain	Impact on total cases and hospitalization	No evidence	No evidence	Secular trends	87% after a single dose, 97% two doses

59% for the second dose, for each city, respectively.[14,27,28] Despite the increase in coverage, estimates remain below those attained for the first dose of measles in the same 2 cities (95% and 91%, respectively) in the same year.[14,27]

IMPACT OF UVV

Decreases in disease, hospitalization and complications in Spain, Greece, Germany and Italy indicate that the UVV strategy has been effective at the national or regional level (Table 2).

In Spain, regions with higher vaccination coverage reported lower hospitalization rates. A temporal decrease of UVV coverage resulted in the reemergence of varicella.[25] The overall hospitalization rate in Spain in 2009 to 2010 was 3.27 per 100,000 and 30.73 per 100,000 for children younger than 5 years of age. In the Navarra region, vaccine effectiveness in preventing laboratory-confirmed varicella in children was estimated at 87% (95% CI: 60–97) after a single dose and 97% (95% CI: 80–100) after 2 doses.[29] Furthermore, UVV in Navarre resulted in an 88% reduction of hospitalization across all ages, between 2006 and 2009.[30] A similar magnitude of effectiveness was reported from the Madrid health region, with an overall 99.0% effectiveness for children 15 months old in the period 2007 to 2009.[31] Interestingly, in Madrid, the temporary withdrawal of this recommendation in 2014 led to an increase in the incidence of 61.8% just 1 year after.[32]

In Greece, a progressive reduction in varicella complications was observed between 2004 and 2012, with age-specific varicella complications decreasing accordingly (www.keelpno.gr; last accessed May 13, 2014). Hospitalization rates due to varicella decreased from 9.1 to 2.4 per 10,000 children.[33]

UVV in Germany led to a 50% reduction of varicella-related hospitalizations and a 70% reduction of all varicella cases. Overall varicella-containing vaccine effectiveness in preventing varicella disease (mild or severe) was 86% (95% CI: 77–92) after dose 1 and 94% (95% CI: 76–99) after dose 2, during a 5-year period.[34] Breakthrough cases increased slightly, but 91% of the cases occurred after dose 1. Indirect protection of unvaccinated children younger than 1 year has also been reported by sentinel health facilities in the Bavaria region with a 43%[14] to 72%[15] decrease of all cases in this age group after UVV. This is consistent with substantial evidence from the US long-running UVV with similar impact.[35]

Regional UVV in Italy has reduced the total number of varicella cases and hospitalizations. In the 8 Italian regions with UVV, a progressively decreasing trend in cases occurred over time. In the Veneto region, from 2004 to 2006, as UVV coverage increased from 12% to 85%, varicella cases decreased from 1600 to 400. These gains were sustained over time with vaccination coverage at 90% in 2011 and 50 varicella cases, with concurrent decreased hospitalization rates.[5] Effectiveness of 1 dose between 2006 and 2012 in the Puglia region was 98.8% in preventing varicella of any severity and 99.0% in preventing severe varicella,[36] although, in that same region, during an outbreak in an elementary school, the vaccine effectiveness was 69.2% (95% CI: 50.5–88.1,[37]) and during an outbreak at a preschool center, the vaccine effectiveness against disease was 82.4%.[38]

Overall, evidence from all 4 countries shows that UVV programs had a large impact in reducing varicella disease burden and provides convincing evidence to address the barriers to widespread UVV implementation described below.

BARRIERS TO UVV IN THE EU

Some European countries have opted not to implement UVV because of one or more barriers related to the implementation of UVV. The barriers include (1) a perceived low disease burden and low public health priority; (2) cost-effectiveness and funding availability; (3) concerns related to a shift in the incidence of varicella disease in older ages and an increase in the incidence of HZ and (4) safety concerns related to MMRV-associated febrile seizures after the first dose. For each of the identified barriers, the issue, evidence to address the barrier and recommendations to overcome the barriers to UVV are presented.

Barrier 1: Perceived Low Disease Burden and Low Public Health Priority

Varicella is frequently perceived as harmless for healthy children and only a severe disease in children with underlying medical conditions. As a consequence, varicella may not be prioritized for prevention by patients, physicians and public health decision makers.

Varicella surveillance practices and the availability of disease burden data vary between EU countries. For example, varicella is not a notifiable disease in the United Kingdom, while it is reportable in Germany and Spain. In France, although varicella is not a mandatory reportable disease, surveillance is performed through the INSERM Sentinelle network. Despite the variation in data quality, varicella has a clear individual and public health burden.[39]

Data from many countries suggest that complications of varicella can be severe and occur in children without underlying medical conditions. In Germany, the burden of varicella complications before the introduction of routine varicella vaccination was 14.1 varicella hospitalizations per 100,000 children, per year.[40] These were predominantly neurologic (25.4%), skin infections (23.2%) and gastrointestinal (15.0%). Importantly, most hospitalizations (77%) occurred in previously healthy children. The annual incidence of neurologic varicella-associated hospitalizations was estimated at 2.4 neurologic complications per 100,000 children.[40] Permanent or possible sequelae were reported in 1.7% and 8.7% of all children, respectively, and 10 varicella-admitted cases resulted in death.[41]

In France, the estimated incidence of varicella was 1200 cases per 100,000 person-years, corresponding to an estimated total of 550,000–750,000 cases each year, representing more than 3500 hospitalizations and approximately 20 deaths. Hospitalizations

and deaths increased with age. Individuals 15 years of age or older represented nearly 10% of all varicella cases, 26% of all varicella-related hospitalizations and 69% of all deaths. For the incidence in nonimmune persons, the lifetime risk ranged from 96%–100%, with a mean case corresponding to 98%.[42]

In Greece, the annual incidence of varicella complications between 1998 and 2002 was estimated at 15.3 per 100,000 children (n = 48). Documented complications included neurologic, skin infections, sepsis, respiratory disorders, gastrointestinal, nephritis, thrombocytopenia and arthritis.[43]

In Spain, the National Epidemiology Centre Carlos III Health Institute report 1998 to 2012 found a mean of 8.6 deaths because of varicella per year (85% in adults over 24 years) and a mean of 17.5 deaths because of HZ per year (90% in adults over 75 years).[44]

Disease burden for varicella in Italy is considered to be 5-fold underestimated because of underreporting.[5] Between 2001 and 2010 in Italy, the mean annual incidence of notifications of varicella was 150.7 cases per 100,000 population, with 948.6 cases per 100,000 in the pediatric age group. In this 10-year period, 20,295 hospitalizations for varicella and 33 varicella-related deaths were reported.[45] Before UVV introduction in any region, Regional Health Authority data estimated 4–5 hospitalizations per 100,000 per annum.[5]

In the United Kingdom, 651,000 varicella cases are estimated to occur per year,[46] with an average incidence between 1991 and 2000 of 1291 cases per 100,000 person-years.[47] Hospitalizations for varicella increased 1.8% from 66.1 to 67.3 per million, with some fluctuations, between 2001/2002 and 2010/2011.[48] Most varicella hospital admissions did not result in severe outcomes, but some severe complications were reported, including bacteremia and septic shock, pneumonia, encephalitis, ataxia, toxic shock syndrome, necrotizing fasciitis, purpura fulminans and disseminated coagulopathy, fulminant varicella and neonatal varicella.[9]

These data indicate that, before the initiation of UVV, the burden of varicella disease, assessed by hospitalizations and complications data, was substantial and broadly similar across all European countries.

Recommendations

The data presented here from several European countries could be used to demonstrate that the burden of varicella is generally similar from one country to the next. If country-specific data are not available, an organized surveillance system for varicella disease and complications with mandatory reporting, such as the one introduced in Germany,[28] would enable better estimates of the true disease burden and facilitate better assessment of the impact of varicella vaccination strategies.

Documentation and communication of disease burden and complications of an otherwise preventable disease with public health officials who have to prioritize the allocation of public funding for universal programs between competing vaccines can raise awareness and support for UVV among other health priorities. Moreover, the effectiveness of varicella vaccine in a specific country's context and the acceptability of a universal program among health care providers and the public are also required for inclusion of varicella vaccines in national immunization programs.

Improving knowledge about the benefits of vaccination and the burden of disease is likely to benefit rates of vaccine acceptance and uptake. Healthcare professionals are responsible for direct communication of health information to the public, and their perception of vaccination programs can influence the recommendation and successful attainment of the UVV public health objectives. As an example, following recommendation and availability of varicella vaccine in Munich in 2006, recommendation by the pediatricians, as reported by the parents, increased from 48% to 60% over the next 3 years, and vaccine coverage increased from 38% to 53%.[27] When evaluating the determinants of parents' acceptance of their child's varicella vaccination, the recommendation by a physician was the most important factor.[27]

Barrier 2: Safety of MMRV After the First Dose

MMRV vaccine has been associated with an increased risk of febrile seizures compared with the separate administration of MMR and varicella vaccine,[49,50] with the effect being similar for both available tetravalent vaccines.[51] Seizure risk during days 7–10 was higher after MMRV than after MMR and varicella, with a relative risk of 1.98 (95% CI: 1.43–2.73) and an excess risk for febrile seizures of 4.3 cases per 10,000 doses (95% CI: 2.6–5.6) in the United States.[50] Similarly, between days 5 and 12 after MMRV, a relative risk of 2.20 (95% CI: 1.04–4.65) was reported.[49] No additional risk of febrile seizure has been found after administration of a second dose of MMRV vaccine.[52]

This safety finding with MMRV vaccine has led to changes in the vaccine schedule in some countries, for example, recommending separate injection of MMR and varicella vaccines for the first dose rather than MMRV. This may have led to subsequent lower assessment of the benefit/risk balance of a UVV program.

Fever-associated seizures occur in 2%–5% of all unvaccinated children between 6 and 60 months of age, with the peak risk occurring at 6–16 months of age.[50] Most convulsions are generalized and last less than 15 minutes. Usually a good prognosis is expected. However, the event is very frightening for parents, and the episode frequently leads to an emergency room visit. The age at the highest background risk of febrile seizures overlaps with the timing recommended for the first dose of MMR and varicella vaccines.[53]

According to the European Centre for Disease Prevention and Control (ECDC), the overall safety profile for varicella-containing vaccines is well established, and the absolute risk of febrile seizures is low (4.3 and 1.2 per 100,000 children vaccinated after the first and second dose, respectively).[50]

Recommendations

Separate administration of MMR and varicella vaccines can be recommended as preferable for the first dose. Although administering MMR and varicella vaccines separately, particularly the first dose, has led to lower coverage rates of varicella vaccination, as transiently observed in Germany,[54] the separation of the vaccines should help to overcome this safety concern and facilitate the introduction of UVV.

Barrier 3: Potential Epidemiologic Impact of Routine Childhood Varicella Immunization Programs on Varicella and HZ

Impact on Varicella

Varicella vaccine is effective in decreasing VZV circulation in the population and consequently lowering exposure to wild-type infection. When exposure to wild-type virus is low, natural boosting of immunized subjects is likely reduced, and subsequently, vaccination or program failures could potentially generate a pool of susceptible individuals. In addition, primary varicella infection in older individuals (eg, adolescents) may lead to more severe disease than infection in young children. A shift in the burden of varicella toward older age groups, as the result of a UVV program, might result in increased morbidity and mortality, despite a potential reduction in the total number of varicella cases.[55–59]

In the United States, no age shift in varicella disease risk has been observed 15 years after implementation of UVV with high 1-dose and 2-dose vaccine coverage.[60] Similarly, data from Germany, Italy, Spain and Greece do not provide evidence of the existence of a shift in burden of varicella to older age groups as a result of UVV. According to data from the Bavaria pediatric hospital surveillance network in Germany, no age shift toward older onset of varicella was observed between 2005 and 2011 after routine vaccination was started in 2006.[28]

Recommendations. High-quality disease surveillance and strong and sustained communication with both the public and with healthcare professionals should be initiated after any UVV is started. To reduce the risk of a shift in varicella disease, World Health Organization and ECDC recommend that when countries or regions decide to introduce UVV, there is sufficient resource allocation to reach and sustain ≥80% vaccination coverage.[12]

Impact on HZ

The most significant concern for implementing UVV is the effect of mass varicella vaccination on the incidence of HZ among subjects that have been infected with the wild-type virus. It has been hypothesized that a lower exposure to circulating varicella virus could lead to waning immune responses and increase the risk of virus reactivation in individuals who have latent VZV because of wild-type infection.[58] Models predict an increased risk of HZ onset in the first decades of a UVV program plus a lower age of HZ onset because of a lack of wild-type boosting. This lack of external immune boosting of adults with latent virus through an infected reservoir of children in the population has been postulated in the United Kingdom as a reason not to implement UVV.[61,62] In addition to the exogenous boosting, there might also be an internal boosting mechanism independent from wild-type virus circulation in the population that protects adults from VZV reactivation. Evidence for that is coming from a publication assessing the risk of HZ in a population with low or no exposure to natural varicella exposure (monks and nuns), which showed no increase in HZ incidence in younger ages than in the general population in France.[63]

No evidence for the association between an increased risk of HZ between vaccinated and unvaccinated subjects and UVV introduction currently exists.

Among subjects with preexisting natural immunity, in general, models predict a transient increase in risk in HZ and lower age of onset upon the introduction of the UVV, followed by a decrease that results in overall benefits. Evidence from different studies using different model techniques is, however, conflicting and dependent upon model assumptions. The mechanism of endogenous boosting is not taken into consideration in models, and studies that only take exogenous boosting into consideration may produce biased results. Moreover, the extent of VZV exposure that is adequate to boost the immunity in those naturally infected is unknown.

A literature review, including 13 publications (7 longitudinal studies and 6 mathematical models), assessed the theoretical impact of UVV on increasing the risk for HZ. Results were discordant, but all models showed a transitory short-term increase in HZ incidence and a long-term reduction of incidence of HZ below the current rate, assuming an effective vaccine and high vaccination coverage.[64] However, results from modeling UVV impact in France showed an overall benefit of UVV introduction in all scenarios of vaccine efficacy, waning immunity levels and vaccination coverage following a slight, transitory increase in HZ after introduction of UVV.[65]

Moreover, real-world evidence from countries that have implemented UVVs indicates only a slight increase of HZ incidence.[66–68] In addition, it has been shown that HZ incidence has increased in many areas in the absence of UVV. Secular trends of increasing incidence of hospitalization have been observed in Germany[69] and in Spain,[70] but these trends began before UVV introduction and were not associated or changed by implementation of the strategy. Furthermore, secular trends toward increased risk of HZ before UVV implementation can be partially explained by secular demographic shifts in the population age structures.[59] Although not associated with the vaccination, these demographic changes may affect the interpretation of potential theoretical increased risk for HZ upon introduction of UVV in studies unable to adjust for the confounders.

Among vaccinated subjects, the currently used 2-dose schedule seems to establish effective and long-lasting humoral and cellular immunity associated with a reduction in the incidence of HZ among pediatric populations. The risk of developing zoster among the vaccinated population has been reported to be significantly lower when compared with that reported in children post-natural varicella,[60,71,72] a finding that could be attributed to the lower viral loads induced by the attenuated vaccine strain[73] and to reduced pathogenic capacity of the OKA strain compared with the wild-type virus. Data from a primary pediatric practice surveillance network in Germany reported no impact of UVV on HZ between October 2006 and September 2011 for children younger than 16 years of age.[74] Similarly, according to unpublished data from the Bavaria pediatric hospital surveillance network in Germany, no marked increased trend of HZ was observed in correlation with the time of UVV introduction. The same has been observed in the United States, which has had a routine vaccine program longer than any other country, as single dose since 1996, updated to 2 dose in 2006. The most recent US data do not show any increase in HZ incidence. One retrospective observational study found that varicella vaccination reduced the incidence of HZ by 79% in children under 18 years of age who received the vaccine (48 per 100,000 person years) relative to individuals who have experienced varicella natural disease (230 per 100,000 person years),[75] while another study reported a protective effect of varicella vaccination on HZ incidence with a relative risk of 0.61 between prevaccine and postvaccine periods.[60]

Recommendations. Overcoming concerns about an increase in HZ after UVV can be addressed by utilizing the available data from countries with ongoing established monitoring systems. Countries can also implement their own monitoring, as recommended by the ECDC. Assembling good-quality data on the incidence of HZ by age groups, before the introduction of UVV, would facilitate a better understanding of the trends of HZ and minimize potential misunderstandings of secular trends before UVV.

This perceived barrier could also be approached with a combined HZ and varicella vaccination strategy, particularly as European countries converge toward HZ vaccination recommendation in the older adults. Strategies including the introduction of HZ vaccination in older adults followed by varicella vaccination during childhood may help overcome the barrier and support the recommendation for UVV.[76]

Barrier 4: Cost-effectiveness and Funding Availability

Cost-effectiveness analyses, including direct vaccination costs, provide little economic support for UVV, and funds for vaccine programs are often limited.

Overall, the economic impact of UVV modeled based on the epidemiologic dynamics of VZV suggests that UVV may be

cost saving from both a societal and a health system perspective, and vaccination remains cost-effective in sensitivity analyses, even using worst-case scenarios, for example, vaccination coverage rates lower than 90%.[77]

For Germany and France, taking a societal perspective, including both direct and indirect costs, Coudeville et al[78] estimated through economical modeling that UVV with a vaccination coverage of 90% could induce cost savings of 61% in Germany and 60% in France. Similarly, the implementation of UVV in Spain was also estimated to be highly cost-effective, on the data and assumptions used.[79] Annual costs because of hospitalization of 1.2 million Euros for children under 10 years and 522,000 over 10 years can be averted.[80] Efficiency studies show a favorable cost-effective relation with ratios 2.1–6.9 when direct (primary-care consults) and indirect (medical prescription) costs are considered.[81–83] An economic assessment of targeting varicella vaccination to varicella-naive 11-year-old children in Italy was also estimated to be cost-effective.[84]

Disease burden estimates used in economic assessments are likely underestimated, and indirect nonmedical costs (eg, parental absenteeism) are often not well accounted for in the cost-effectiveness models. In addition, models that consider exogenous boosting for protection of VZV reactivation only could provide biased underestimates on the benefit of UVV, by overweighting the role of wild-type boosting.[57,58]

Recommendations

Cost-effectiveness models could be improved by including indirect nonmedical costs such as parental absenteeism to evaluate the wider financial savings provided by the vaccine, as well as the overall benefits in the long term rather than overfocusing on the transitory period of implementation of the UVV until the entire population is immunized.

A reduction in the vaccine price, if decided, could render more favorable cost-effectiveness assessments.

CONCLUSION

Countries in Europe and other parts of the world have demonstrated significant public health impact after implementing a UVV program. Reductions of up to 80% have been shown in varicella disease incidence, hospitalizations and complications, indicating that the strategy has been effective at both national and regional levels. To move varicella forward as a truly vaccine-preventable disease, the key barriers addressed here need to be overcome. Improvements in VZV surveillance, dissemination of existing evidence generated from long-standing UVV programs in many parts of Europe and the United States, and better communication of the risks and benefits of varicella vaccination to public health decision-makers, healthcare professionals and the general public are all effective methods to overcome these concerns.

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