

## Implementing universal varicella vaccination in Europe: The path forward.

Vana Spoulou, MD <sup>1,#</sup>, Sophie Alain, MD <sup>2</sup>, Giovanni Gabutti, MD <sup>3</sup>, Carlo Giaquinto, MD <sup>4</sup>, Johannes Liese, MD <sup>5</sup>, Eithne MacMahon, MD <sup>6</sup>, Federico Martinon-Torres, MD <sup>7</sup>, Timo Vesikari, MD <sup>8</sup>,

<sup>1</sup> Aghia Sophia Children's Hospital, Athens University School of Medicine, Athens, Greece,

vspoulou@med.uoa.gr

<sup>2</sup> National Reference Center for Herpesviruses, University Hospital Limoges, 2 avenue Martin Luther King 87042 LIMOGES, France, sophie.alain@chu-limoges.fr

<sup>3</sup> Department of Medical Sciences, University of Ferrara, 44121 Ferrara, Italy, giovanni.gabutti@unife.it

<sup>4</sup> Department of Paediatrics, University of Padua, Via Giustiniani 3 PADOVA 35128, Italy,

carlo.giaquinto@unipd.it

<sup>5</sup> Paediatric Infectious Diseases and Immunology, University Children's Hospital Josef-Schneider-Straße 2, 97080 Würzburg, Germany, Liese\_J@ukw.de

<sup>6</sup> Department of Infectious Diseases, St. Thomas' Hospital, Guy's & St. Thomas' NHS Foundation Trust, London, United Kingdom, UK, eithne.macmahon@kcl.ac.uk

<sup>7</sup> Translational Pediatrics and Infectious Diseases, Hospital Clínico Universitario de Santiago, Unidad de Investigación en vacunas, IDIS, Santiago, Spain, federico.martinon.torres@sergas.es

<sup>8</sup> University of Tampere Medical School, Biokatu 10, 33014, Tampere, Finland, timo.vesikari@uta.fi

# Corresponding author: Vana Spoulou, Aghia Sophia Children's Hospital, Athens University School of Medicine, Thivon & Papadiamantopoulou, Goudi, Athens 115 27, Greece, tel. 00306944149266, e-mail - vspoulou@med.uoa.gr

**Acknowledgements:** Germano Ferreira for editorial support and, Barbara Kuter for significant contributions to the paper.

## **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) theoretical considerations related to a shift in varicella disease and incidence of HZ, and 4) safety concerns related to MMRV-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 paper discusses ways to overcome the barriers to move varicella forward as a truly vaccine preventable disease.

## Introduction (word count 368)

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

In young children, VZV usually presents as a mild disorder, but severe complications of varicella can occur. The risk of varicella complications increases with age (4). Complications include skin and soft tissue superinfections as well as neurological and pulmonary conditions. Fatalities are rare, 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 ("shingles"; HZ). The disease affects dermatomes located in the proximity of the site of viral reactivation. Post-herpetic neuralgia (PHN), a severe and often long-lasting pain, is a common complication (7). Other neurological complications include facial palsy, encephalitis, and cerebral vasculitis (8). The risk of HZ increases with age, but can occur at any age, particularly in those immunosuppressed.

Varicella vaccine is well tolerated but contraindicated in persons with immunosuppression and in the first year of life (4). The vaccine is highly efficacious at 80% efficacy after two-doses - particularly for the prevention of severe disease (9). The vaccine effectiveness of a two-dose regimen in routine use is as high as 98% (10). The two available varicella vaccines in Europe, (Varivax™ and Varilrix™), consist of the live attenuated Oka vaccine strain (8) and are indicated in one or two dose regimens, dependent on the licensed indication or country specific recommendations (11).

WHO recommends varicella vaccination for adolescents and adults without a history of varicella, and those at increased risk of contracting or transmitting VZV. For countries where varicella is an important health burden, WHO recommends that if sufficient resources exist to reach and sustain a vaccine coverage level of  $\geq 80\%$ , the introduction of varicella vaccination in the routine childhood immunization programme should be considered (11).

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 UVV and proposes ways to overcome these barriers by comparing countries with and without UVV.

## Status of varicella vaccination in the EU (word count 713)

In the EU, recommendations for and implementation of UVV vary widely. The first European country to incorporate national-level UVV with a one dose schedule was Germany in 2004 (12), twenty years after the Oka strain vaccine was first licensed in 1984 in Japan(13). UVV recommendations were adjusted to a two-dose schedule in Germany in 2009 as a result of evidence of continued varicella virus circulation and occurrence of varicella outbreaks. (12) In 2006, a measles, mumps, rubella, and varicella (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. (13, 14).

Monovalent varicella vaccines are available in all 28 EU member countries and as 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 six are implemented as publicly funded UVV programs.

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 (ref 23 in (5)). Varicella vaccination was included in the Italian National Plan for Vaccination in 2005-2007 for persons at high-risk of complications and susceptible adolescents (15). Italy's National Plan for Vaccination (2017-2019) recommends UVV at the national following on the experience from existing regional programs (16). In mid 2017 varicella vaccination has been made compulsory as well as those against measles, mumps and rubella, and those included in the hexavalent vaccine (17).

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 12-15 months onwards (with one or two doses). In the rest of the Spain, only high-risk patients and rescue vaccination by the age of 12 with two doses of the vaccine was reimbursed (18). Parent followed paediatricians' 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 non-hospitalized population access to varicella vaccine in community pharmacies (19). Subsequently Spain's Ministry of Health announced the inclusion of universal childhood varicella vaccination in the national immunization program beginning in 2016 (20).

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 UK 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 post-exposure prophylaxis (PEP) vaccination is used in specific circumstances (21).

In the UK, re-evaluation of the guidelines was initiated in 2015 by the Joint Committee on Vaccination and Immunisation (JVCI) and is currently ongoing. In France, Souty and colleagues 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)(22); 2) the limited effectiveness of PEP (62%), in France, when PEP is administered within 3-5 days after varicella exposure in susceptible subjects(22); 3) the high probability of infection in susceptible adults after exposure through familial contact (32% of 221 adults) (22); and 4) the finding that among the 35% of 18 years old with uncertain varicella history, 11% were truly non-immune. 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% (22).

#### Vaccination coverage following 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) (23). Following the restriction to hospital use in 2014, the nationwide vaccination coverage dropped from 45% in 2012, to 31% in 2013 to 2% in 2014. Greece obtained UVV one-dose coverage above 70% among 6-7 years old, in 2012 with age appropriate vaccination being completed by 61% of pre-schoolers in Athens (24).

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 two cities in Bavaria had reached 83% and 68% for the first dose, and 72% and 59% for the second dose, for each city respectively (12, 25, 26). Despite the increase in coverage, estimates remain below those attained for the first dose of measles in the same two cities (95% and 91% respectively) in the same year (12, 25).

#### **Evidence on the impact of universal varicella vaccination (word count 585)**

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 (27). A temporal decrease of UVV coverage resulted in the re-emergence of varicella. Incidence increased from approximately 315 (2012, 2013) to 350 per 100 000 inhabitants by 2013 [REF]. The overall hospitalization rate in Spain in 2009-2010 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 two doses (28). Furthermore, UVV in Navarre resulted in a >90% reduction of hospitalization and a 98.5 decrease in the vaccinated, across all ages of children 0 to 9 years old, between 2006 and 2012 (28). 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 2007-2009.(29)

In Greece, a progressive reduction in varicella complications was observed between 2004 and 2012, with age-specific varicella complications decreasing accordingly [ref [www.keelpno.gr](http://www.keelpno.gr), last accessed 13/5/14]. Hospitalization rates due to varicella decreased from 9.1 to 2.4 per 10 000 children. Hospitalization due to HZ was 0.1 pre-vaccination and 0 post-vaccination per 10 000 children (30).

UUV in Germany led to a 50% reduction of varicella related hospitalizations, and a 70% reduction of all varicella cases. Overall varicella-containing vaccines effectiveness in preventing varicella disease (mild or severity) was 86% (95% CI 77-92) after dose 1 and 94% (95% CI: 76-99) after dose 2, during a 5-year period (31). Breakthrough cases increased slightly, but 91% occurred after dose 1. Indirect protection of unvaccinated children <1 year seems to be provided by herd immunity, as is suggested by the decrease of all cases and hospitalizations in this age group after UUV introduction. This is consistent with substantial evidence from the US long-running UUV with similar impact. Sentinel health facilities in the Bavaria region of Germany found decreases in cases of varicella between 2006 and 2011 of 74% (total n=16054). This decrease was observed in vaccinated (5-16 years) and unvaccinated (< 1 year) age-groups, with the reduction of cases in the <1 year age group (71%) indicating indirect protection conferred by the UUV program (12). In the same region and time period, a 72% decrease in hospitalization was observed (13). From 1995-2002 age-adjusted annual estimates decreased from 3.3 to 1.9 per 100,000 persons from the pre- to post- vaccination era across Germany.(32)

Regional UUV in Italy has reduced the total number of varicella cases as well as hospitalizations. In the 8 Italian regions with UUV, a progressively decreasing trend in cases occurred over time. In the Veneto region, from 2004 to 2006, as UUV 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 one 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 (33).



Overall, evidence from all four countries shows that UVV programs had a large impact in reducing varicella disease burden, and that there is no evidence to support the concerns which have constituted barriers to widespread UVV implementation described below.

## **Barriers to UVV in the EU**

Some European countries have opted not to implement UVV due to 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) theoretical considerations 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.

#### Evidence to address this barrier

Varicella surveillance practices and the availability of disease burden data vary between EU countries. For example, varicella is not a notifiable disease in the UK, 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, it is clear that varicella has a relatively high individual and public health burden (34).

Data from many countries suggest that complications of varicella can be severe and occur in children without underlying medical conditions. For example, in Germany during 2003-2004, complications were reported in 80% of varicella hospitalizations (n=918). These were predominantly neurologic (25.4%), skin infections (23.2%), and gastrointestinal (15.0%). Importantly, most hospitalizations (77%) occurred in

previously healthy children. Permanent or possible sequelae were reported in 1.7% and 8.7% of all children, respectively, and in ten varicella-admitted cases resulted in death. The annual incidence of neurologic complications was estimated at 2.4 per 100 000 children (35); 14.1 per 100 000 cases resulted in hospital admission (36).

In France, the estimated incidence of varicella was 1200 cases per 100 000 person-years, corresponding to an estimated total of 550 000 to 750 000 cases each year, representing more than 3500 hospitalizations and approximately 20 deaths. Hospitalizations and deaths increased with age. Individuals aged 15 years or older represented 8.3% of all varicella cases, 26% of all varicella-related hospitalizations, and 69% of all deaths. In addition, 10.3% of people  $\geq$  15 years old were susceptible to VZV infection, and 79% of them were expected to contract varicella during their lifetime. Over a ten-year period, annual hospitalization rates for varicella increased by 1.8%, with fluctuations, from 66.1 to 67.3 per million people.

In Greece, the annual incidence of varicella complications between 1998 - 2002 was estimated at 15.3 per 100 000 children (n=498). Documented complications included neurological, skin infections, sepsis, respiratory disorders, gastrointestinal, nephritis, thrombocytopenia and arthritis (37).

In Spain, the National Epidemiology Centre Carlos III Health Institute report 1998-2012, found a mean of 8.6 deaths due to varicella per year (85% in adults over 24 years) and a mean of 17.5 deaths due to HZ per year (90% in adults over 75 years) (38).

Disease burden for varicella in Italy is considered to be 5-fold underestimated due to 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 paediatric age group. In this ten-year period, 20 295 hospitalizations for varicella and 33 varicella-related deaths were reported (39). Prior to UVV introduction in any region, Regional Health Authority data estimated  $\sim$ 4-5 hospitalizations per 100 000 per annum (5).

In the UK, 651 000 varicella cases are estimated to occur per year (40), with an average incidence between 1991 and 2000 of 1 291 cases per 100 000 person-years (41). Hospitalizations for varicella increased 1.8% from 66.1 to 67.3 per million, with some fluctuations, between 2001/2002 and 2010/2011 (42). Most varicella hospital admissions did not result in severe outcomes, but some severe complications were reported including bacteraemia and septic shock, pneumonia, encephalitis, ataxia, toxic shock syndrome, necrotising fasciitis, purpura fulminans and disseminated coagulopathy, fulminant varicella and neonatal varicella (4).

These data indicate that, prior to 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 (26), 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 can raise awareness and support for UVV amongst general practitioners, public health officials, and the public.

Improving knowledge about the benefits of vaccination and the burden of disease is likely to benefit rates of vaccine acceptance and uptake. Health care 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 paediatricians, as reported by the parents, increased from 48% to 60% over the next 3 years, and vaccine

coverage increased from 38% to 53% (25). When evaluating the determinants of parents' acceptance of their child's varicella vaccination, the recommendation by a physician were the most important factor (25).

### ***Barrier 2: Safety of MMRV after the first dose***

MMRV vaccine has been associated with a small increased risk of febrile seizures compared with the separate administration of MMR and varicella vaccine (41, 42), with the effect being similar for both available tetravalent vaccines (43). Use of the combination MMRV vaccine instead of MMR and varicella vaccines for the first dose has been found to have an additional risk of about 1 more febrile seizure for each ~2500 children vaccinated (41). No additional risk of febrile seizure has been found following administration of a second dose of MMRV vaccine.

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

### **Evidence to address this barrier**

Fever-associated seizures occur in 2-5% of all unvaccinated children between 6-60 months old, with the peak risk occurring at 6-16 months of age (43). Most convulsions are generalized and last less than 15 minutes. A good prognosis is expected without association with long-term sequelae. However, the event is very frightening for parents and the episode frequently leads to an emergency room visit. The age at highest background risk of febrile seizures overlaps with the timing recommended for the first dose of MMR and varicella vaccines (44).

According to the ECDC, the overall safety profile for varicella-containing vaccines is well established and the absolute risk of febrile seizures is low. The absolute risk of febrile seizures attributed to the MMRV vaccine is low at 4.3 (95% CI 2.6-5.6) and 3.8 (95% CI 0.3-7.4) per 10 000 children vaccinated after the first

dose, and 1.2 (95% CI 0.03-6.4) per 100 000 children vaccinated after the second dose (43). No unusual sequelae have been reported in these children.

### Recommendations

Separate administration of MMR and V 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 (45), the separation of the vaccines should help to overcome this safety concern and facilitate the introduction of UVV.

### ***Barrier 3: Potential epidemiological impact of routine childhood varicella immunization programmes on varicella and Herpes zoster***

#### ***a) 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 programme failures could potentially generate a pool of susceptible individuals. In addition, primary varicella infection in older individuals (e.g. adolescents) may lead to more severe disease than infection in young children. A shift in the burden of varicella towards 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 (46-50).

### Evidence to address this barrier

In the USA, no age shift in varicella disease risk has been observed 15 years after implementation of UVV with high one and two dose vaccine coverage (51). Data from Germany, Italy, Spain and Greece do not provide any conclusive 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 paediatric hospital surveillance network in Germany, no

age shift towards older onset of varicella was observed between 2005 and 2011 after routine vaccination was started in 2006 (26).

### 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, WHO and ECDC recommend that when countries or regions decide to introduce UVV that there is sufficient resource allocation to rapidly reach and sustain  $\geq 80\%$  vaccination coverage (11).

#### ***b) Impact on Herpes Zoster***

It has been hypothesized that a lower exposure to circulating wild-type varicella virus could lead to a waning immune response and increased risk of virus activation in individuals who are unprotected by vaccination and have latent varicella zoster virus due to wild-type infection (52). This scenario could possibly lead to an increased risk of HZ onset in the first decades of a UVV program plus a lower age of HZ onset due to a lack of wild-type boosting. This lack of immune boosting of adults with latent virus through an infected reservoir of children in the population has been postulated in the UK as a reason not to implement UVV (53, 54).

### Evidence to address this barrier

No evidence for the association between an increased risk of HZ and UVV introduction currently exists. In general, models predict a transient increase 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 are, however, conflicting and dependent upon model assumptions.

A literature review including 13 publications (seven longitudinal studies and six 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 (55). Results from modelling UVV impact in France (56) showed an overall benefit of UVV introduction in all scenarios of vaccine efficacy, waning immunity levels, and vaccination coverage, despite a slight, transitory increase in HZ after introduction of UVV. A publication assessing the risk of HZ in a population with low or no exposure to natural varicella exposure (monks and nuns), showed no increase in HZ incidence in younger ages than in the general population in France (57). This finding indicated that in addition to the exogenous boosting there might also be an internal boosting mechanism independent from wild-type virus circulation in the population. The latter mechanism of endogenous boosting is not taken into consideration in models, and studies that only take exogenous boosting into consideration (disregarding endogenous boosting) may produce biased results.

Secular trends of increasing incidence of varicella hospitalization have been observed in Germany (58) and in Spain (59), but these trends began before UVV introduction, and were not associated or changed by implementation of the strategy. Furthermore, secular trends towards increased risk of HZ before UVV implementation can be partially explained by secular demographic shifts in the population age structures(49). 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.

No impact of UVV on HZ was observed in a primary paediatric practice surveillance network in Germany between October 2006 and September 2011 for children younger than 16 years of age (60). Similarly, according to unpublished data from the Bavaria paediatric 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 USA which has had a routine vaccine program longer than any other country, as single dose since 1996, updated to two-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 individuals within the population that received the vaccine (48 per 100,000



person years) relative to individuals who have experienced varicella natural disease (230 per 100 000 person years) (61) while another study reported a protective effect of varicella vaccination on HZ incidence with a relative risk of 0.61 (95% CI: 0.43-0.89) between pre-vaccine and post-vaccine periods (51).

### Recommendations

Overcoming concerns about an increase in herpes zoster 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, prior to the introduction of UVV, would facilitate a better understanding of the trends of HZ and minimize potential misunderstandings of secular trends prior to UVV.

This perceived barrier could also be approached with a combined HZ and Varicella vaccination strategy, particularly as European countries converge towards 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 (62).

### ***Barrier 4: Cost-effectiveness and funding availability (word count 156)***

Cost-effectiveness analyses often provide little economic support for UVV and funds for vaccine programs are often limited.

### Evidence to address this barrier

Overall the economic impact of UVV modelled based on the epidemiological dynamics of varicella zoster virus 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, e.g. vaccination coverage rates lower than 90% (63).

For Germany and France, taking a societal perspective, including both direct and indirect costs, Coudeville et al. estimated through economical modelling, that UVV with a vaccination coverage of 90% could induce

cost savings of 61% in Germany and 60% in France (64). Similarly, the implementation of UVV in Spain was also estimated to be highly cost-effective, on the data and assumptions used (65).

In Spain, annual costs due to hospitalisation of 1.2 million euros for children under 10 years and 522,000 over 10 years can be averted (66). Efficiency studies show a favourable cost-effective relation with ratios 2.1-6.9 when direct (primary care consults) and indirect (medical prescription) costs are considered (67-69).

An economic assessment of targeting Varicella vaccination to varicella-naïve 11-year old children in Italy, was also estimated to be cost-effective (70).

Disease burden estimates used in economic assessments are likely underestimated and indirect non-medical costs (e.g. parental absenteeism) are often not well accounted for in the cost-effectiveness models. In addition, models that consider exogenous boosting only could provide biased underestimates on the benefit of UVV, by overweighting the role of wild-type boosting (48, 50).

### Recommendations

Cost-effectiveness models could be improved by including indirect non-medical 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 over-focusing on the transitory period of implementation of the UVV until the entire population is immunized.

Varying the price of the vaccine could also render more favourable cost-effectiveness assessments.

### **Conclusion (word count 138)**

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 part of Europe and the US, and better communication of the risks and benefits of varicella vaccination to public health decision makers, health care professionals, and the general public are all effective methods to overcome these concerns.

**Conflicts of Interest and Source of Funding:**

VS declares financial compensation for travel costs, presentations at medical congresses, and participation at advisory boards (GSK, SP-MSD,) and study grants from Sanofi Pasteur MSD for clinical studies related to prevention and epidemiology of pediatric infectious diseases .

SA is a member of advisory boards of GSK, MSD, Sanofi, Shire, and Biotest, and is PI for a rescue therapy protocol sponsored by Shire but did not receive honorarium for this.

GG received grants from Sanofi Pasteur MSD, GSK Biologicals SA, Novartis, Crucell/Janssen, Pfizer, Sanofi Pasteur, MSD Italy and Seqirus for taking part in advisory boards, expert meetings, for acting as speaker and/or organizer of meetings/congresses and as principal investigator and chief of O.U. in RCTs.

FMT received honoraria from GSK, Pfizer, Sanofi Pasteur, MSD, and Janssen for taking part in advisory boards, expert meetings and for acting as speaker in congresses outside of the submitted work and paid to his institution. FMT has also acted as principal investigator in RCTs of the above-mentioned companies as well as Seqirus, Ablynx, Regeneron, and Medimmune.

CG received consultancy and research grants to his referral Institutions from SPMSD, Merck, GSK-Bio, Gilead, ViiV-Healthcare;

JL declares financial compensation for travel costs, presentations at medical congresses, and participation at advisory boards (GSK group of companies, SP-MSD, Pfizer, Novartis); study grants for different studies related to prevention and epidemiology of pediatric infectious diseases (GSK group of companies, Pfizer).

EMM has received sponsorship from Aventis Pasteur MSD towards attending conferences in the past five years.

TV is a member of advisory boards for Sanofi Pasteur MSD, Merck, and Novartis and a consultant for Pfizer; he has received honoraria or lecture fees from the same and GSK.

## References

1. Guess HA, Broughton DD, Melton LJ, 3rd, Kurland LT. Population-based studies of varicella complications. *Pediatrics*. 1986;78:723-727.
2. Gordon JE. Chickenpox: an epidemiological review. *Am J Med Sci*. 1962;244:362-389.
3. Bollaerts K, Riera-Montes M, Heininger U, et al. A systematic review of varicella seroprevalence in European countries before universal childhood immunization: deriving incidence from seroprevalence data. *Epidemiol Infect*. 2017;1-12.
4. Cameron JC, Allan G, Johnston F, Finn A, Heath PT, Booy R. Severe complications of chickenpox in hospitalised children in the UK and Ireland. *Arch Dis Child*. 2007;92:1062-1066.
5. Bechini A, Boccalini S, Baldo V, et al. Impact of universal vaccination against varicella in Italy. *Hum Vaccin Immunother*. 2015;11:63-71.
6. Riera-Montes M, Bollaerts K, Heininger U, et al. Estimation of the burden of varicella in Europe before the introduction of universal childhood immunization. *BMC Infect Dis*. 2017;17:353.
7. Kost RG, Straus SE. Postherpetic neuralgia--pathogenesis, treatment, and prevention. *N Engl J Med*. 1996;335:32-42.
8. Norberg P, Depledge DP, Kundu S, et al. Recombination of Globally Circulating Varicella-Zoster Virus. *J Virol*. 2015;89:7133-7146.
9. Heininger U, Seward JF. Varicella. *Lancet*. 2006;368:1365-1376.
10. Shapiro ED, Vazquez M, Esposito D, et al. Effectiveness of 2 doses of varicella vaccine in children. *J Infect Dis*. 2011;203:312-315.
11. Varicella and herpes zoster vaccines: WHO position paper, June 2014. *Wkly Epidemiol Rec*. 2014;89:265-287.
12. Streng A, Grote V, Carr D, Hagemann C, Liese JG. Varicella routine vaccination and the effects on varicella epidemiology - results from the Bavarian Varicella Surveillance Project (BaVariPro), 2006-2011. *BMC Infect Dis*. 2013;13:303.

13. Streng A HS, Bungartz C, Grote V, Liese J. Rückgang von Varizella-zoster-Virus-assoziierten Hospitalisationen und Komplikationen nach Einführung der Varizellenimpfung bei Kindern in Bayern. *Monatsschr Kinderheilkd [Internet]*2011.
14. The Standing Committee on Vaccination (STIKO) at the Robert Koch Institute. Zur Kombinationsimpfung gegen Masern, Mumps, Röteln und Varizellen (MMRV). *Epidemiologisches Bulletin*. 2011;38:352-353.
15. Ministero della Salute. Piano Nazionale Prevenzione Vaccinale 2005-2007.
16. Ministero della Salute. Piano Nazionale Prevenzione Vaccinale 2017-2019.
17. Ministero della Salute. Circolare recante prime indicazioni operative per l'attuazione del decreto-legge 7 giugno 2017, n.73, recante "Disposizioni urgenti in materia di prevenzione vaccinale" 2017.
18. Ministerio de Sanidad Servicios Sociales e Igualdad. Resolución de 24 de julio de 2013, de la Dirección General de Salud Pública, Calidad e Innovación, por la que se publica el Acuerdo del Consejo Interterritorial del Sistema Nacional de Salud sobre el calendario común de vacunación infantil. *Boletín Oficial del Estado*. 2013;187:57629.
19. Ministerio de Sanidad Servicios Sociales e Igualdad. Todas las personas a las que el médico les prescriba la vacuna de la varicela fuera de calendario por algún riesgo concreto tendrán acceso a ella de forma gratuita en el hospital. 2014.
20. Ministerio de Sanidad Servicios Sociales e Igualdad. Las Comunidades Autónomas acuerdan vacunar de la varicela en la edad pediátrica temprana. In: Ministerio de Sanidad SseI, ed.2015.
21. Varicella. *The green book*: Public Health England; 2015.
22. Souty C, Boos E, Turbelin C, Blanchon T, Hanslik T, Boelle PY. Vaccination against varicella as post-exposure prophylaxis in adults: a quantitative assessment. *Vaccine*. 2015;33:446-450.
23. Gil-Prieto R, Garcia-Garcia L, San-Martin M, Gil-de-Miguel A. Varicella vaccination coverage inverse correlation with varicella hospitalizations in Spain. *Vaccine*. 2014;32:7043-7046.
24. Pavlopoulou ID, Michail KA, Samoli E, Tsiftis G, Tsoumakas K. Immunization coverage and predictive factors for complete and age-appropriate vaccination among preschoolers in Athens, Greece: a cross-sectional study. *BMC Public Health*. 2013;13:908.

25. Streng A, Seeger K, Grote V, Liese JG. Varicella vaccination coverage in Bavaria (Germany) after general vaccine recommendation in 2004. *Vaccine*. 2010;28:5738-5745.
26. Hecht J, Siedler A. The epidemiology of varicella disease in Germany after introduction of a vaccination recommendation - Analysis of mandatory and sentinel data between 2002 and 2014. *Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz*. 2017;60:118-126.
27. Garcia Cenoz M, Castilla J, Chamorro J, et al. Impact of universal two-dose vaccination on varicella epidemiology in Navarre, Spain, 2006 to 2012. *Euro Surveill*. 2013;18:20552.
28. Cenoz MG, Martinez-Artola V, Guevara M, Ezpeleta C, Barricarte A, Castilla J. Effectiveness of one and two doses of varicella vaccine in preventing laboratory-confirmed cases in children in Navarre, Spain. *Hum Vaccin Immunother*. 2013;9:1172-1176.
29. Ministerio de Sanidad Servicios Sociales e Igualdad. Revisión de las recomendaciones de vacunación frente a varicela en grupos de riesgo. Madrid, España 2015.
30. Critselis E, Klinaki E, Koutsoubari I, et al. Impact of routine Varicella immunization on varicella infection and Herpes zoster incidence rates among children and adolescents in Greece. In: Roilides E, ed. *30th Annual ESPID Meeting*. Thessaloniki, Greece 2012:856.
31. Liese JG, Cohen C, Rack A, et al. The effectiveness of varicella vaccination in children in Germany: a case-control study. *Pediatr Infect Dis J*. 2013;32:998-1004.
32. Siedler A, Arndt U. Impact of the routine varicella vaccination programme on varicella epidemiology in Germany. *Euro Surveill*. 2010;15:pii: 19530.
33. Tafuri S, Fortunato F, Cappelli MG, et al. Effectiveness of vaccination against varicella in children under 5 years in Puglia, Italy 2006-2012. *Hum Vaccin Immunother*. 2015;11:214-219.
34. Balabanova Y, Gilsdorf A, Buda S, et al. Communicable diseases prioritized for surveillance and epidemiological research: results of a standardized prioritization procedure in Germany, 2011. *PLoS One*. 2011;6:e25691.
35. Rack AL, Grote V, Streng A, et al. Neurologic varicella complications before routine immunization in Germany. *Pediatr Neurol*. 2010;42:40-48.

36. Liese JG, Grote V, Rosenfeld E, et al. The burden of varicella complications before the introduction of routine varicella vaccination in Germany. *Pediatr Infect Dis J.* 2008;27:119-124.
37. Theodoridou M, Laina I, Hadjichristodoulou C, Syriopoulou V. Varicella-related complications and hospitalisations in a tertiary pediatric medical center before vaccine introduction. *Eur J Pediatr.* 2006;165:273-274.
38. Torres de Mier M, Ciaravino G, Sagrado Benito M, Martínez de Aragón Esquivias M, Masa Calles J, Red Nacional de Vigilancia Epidemiológica (RENAVE). SITUACIÓN DE LA VARICELA Y DEL HERPES ZÓSTER EN ESPAÑA, 1998-2012. *Boletín Epidemiológico Semanal.* 2014;22.
39. Trucchi C, Gabutti G, Rota MC, Bella A. Burden of varicella in Italy, 2001-2010: analysis of data from multiple sources and assessment of universal vaccination impact in three pilot regions. *J Med Microbiol.* 2015;64:1387-1394.
40. Brisson M, Edmunds WJ. Epidemiology of Varicella-Zoster Virus in England and Wales. *J Med Virol.* 2003;70 Suppl 1:S9-14.
41. Brisson M, Edmunds WJ. Varicella vaccination in England and Wales: cost-utility analysis. *Arch Dis Child.* 2003;88:862-869.
42. Abdalrahman B, Laverty AA, Beckett G, Majeed A. Trends in hospital admissions for Varicella and Zoster viruses in England, 2001/2002-2010/2011: time trend study. *JRSM Open.* 2015;6:2054270414562984.
43. Klein NP, Fireman B, Yih WK, et al. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. *Pediatrics.* 2010;126:e1-8.
44. Gabutti G, Kuhdari P, Ferioli S, Trucchi C. Hospital admissions for seizure in Italy: a decennial retrospective analysis with a special focus on the burden in the pediatric age. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology.* 2015;36:1667-1673.
45. Streng A, Liese J. Decline of varicella vaccination in German surveillance regions after recommendation of separate first-dose vaccination for varicella and measles-mumps-rubella. *Vaccine.* 2014;32:897-890.



46. Brisson M, Edmunds WJ, Gay NJ, Miller E. Varicella vaccine and shingles. *JAMA*. 2002;287:2211; author reply 2211-2212.
47. Edmunds WJ, Brisson M, Gay NJ, Miller E. Varicella vaccination: a double-edged sword? *Commun Dis Public Health*. 2002;5:185-186.
48. Guzzetta G, Poletti P, Merler S, Manfredi P. The Epidemiology of Herpes Zoster After Varicella Immunization Under Different Biological Hypotheses: Perspectives From Mathematical Modeling. *Am J Epidemiol*. 2016;183:765-773.
49. Marziano V, Poletti P, Guzzetta G, Ajelli M, Manfredi P, Merler S. The impact of demographic changes on the epidemiology of herpes zoster: Spain as a case study. *Proc Biol Sci*. 2015;282:20142509.
50. Poletti P, Melegaro A, Ajelli M, et al. Perspectives on the impact of varicella immunization on herpes zoster. A model-based evaluation from three European countries. *PLoS One*. 2013;8:e60732.
51. Baxter R, Ray P, Tran TN, et al. Long-term effectiveness of varicella vaccine: a 14-Year, prospective cohort study. *Pediatrics*. 2013;131:e1389-1396.
52. Field N, Amirthalingam G, Waight P, et al. Validity of a reported history of chickenpox in targeting varicella vaccination at susceptible adolescents in England. *Vaccine*. 2014;32:1213-1217.
53. Rohn J. What's the real reason Britons aren't offered the chickenpox vaccine? 2014 May 15 2014. Available at: <https://www.theguardian.com/science/occams-corner/2014/may/15/realreason-british-public-chickenpox-vaccine-shingles>.
54. Edmunds WJ, Brisson M. The effect of vaccination on the epidemiology of varicella zoster virus. *J Infect*. 2002;44:211-219.
55. Alain S, Paccalin M, Larnaudie S, Perreaux F, Launay O. Impact de la vaccination de routine de l'enfant contre la varicelle sur l'épidémiologie du zona. *Médecine Mal Infect*. 2009;39:698-706.
56. Ouwens MJ, Littlewood KJ, Sauboin C, et al. The impact of 2-dose routine measles, mumps, rubella, and varicella vaccination in France on the epidemiology of varicella and zoster using a dynamic model with an empirical contact matrix. *Clin Ther*. 2015;37:816-829 e810.
57. Gaillat J GV, Launay O, Malvy D, Demoures B, Lewden L, et al. Does monastic life predispose to the risk of Saint Anthony's fire (herpes zoster)? *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2011;53:405-410.

58. Siedler A, Dettmann M. Hospitalization with varicella and shingles before and after introduction of childhood varicella vaccination in Germany. *Hum Vaccin Immunother.* 2014;10:3594-3600.
59. Esteban-Vasallo MD, Dominguez-Berjon MF, Gil-Prieto R, Astray-Mochales J, Gil de Miguel A. Temporal trends in herpes zoster-related hospitalizations in Madrid (Spain), 2003-2013. *J Infect.* 2015;71:85-92.
60. Streng A, Hanke S, Grote V, Liese JG. Decline of Herpes Zoster cases < 10 years of age after introduction of routine varicella vaccination in Bavaria, 2006-2011. In: Esposito S, ed. *31th Annual ESPID Meeting.* Milan, Italy 2013:1161.
61. Weinmann S, Chun C, Schmid DS, et al. Incidence and clinical characteristics of herpes zoster among children in the varicella vaccine era, 2005-2009. *J Infect Dis.* 2013;208:1859-1868.
62. Vazquez M, Shapiro ED. Varicella vaccine and infection with varicella-zoster virus. *N Engl J Med.* 2005;352:439-440.
63. Coudeville L, Brunot A, Giaquinto C, Lucioni C, Dervaux B. Varicella vaccination in Italy : an economic evaluation of different scenarios. *Pharmacoeconomics.* 2004;22:839-855.
64. Coudeville L, Brunot A, Szucs TD, Dervaux B. The economic value of childhood varicella vaccination in France and Germany. *Value Health.* 2005;8:209-222.
65. Lenne X, Diez Domingo J, Gil A, Ridao M, Lluch JA, Dervaux B. Economic evaluation of varicella vaccination in Spain: results from a dynamic model. *Vaccine.* 2006;24:6980-6989.
66. Gil A, Gonzalez A, Oyaguez I, Martin MS, Carrasco P. The burden of severe varicella in Spain, 1995--2000 period. *European journal of epidemiology.* 2004;19:699-702.
67. Diez Domingo J, Ridao M, Latour J, Ballester A, Morant A. A cost benefit analysis of routine varicella vaccination in Spain. *Vaccine.* 1999;17:1306-1311.
68. Salleras L, Domínguez A, Navas E. Efficacy, effectiveness and efficiency of the varicella vaccine. *Vacunas Invest Pract* 2001;2:12-15.
69. Diez-Domingo J, Aristegui J, Calbo F, et al. Epidemiology and economic impact of varicella in immunocompetent children in Spain. A nation-wide study. *Vaccine.* 2003;21:3236-3239.

70. Thiry N, Beutels P, Tancredi F, et al. An economic evaluation of varicella vaccination in Italian adolescents. *Vaccine*. 2004;22:3546-3562.

Table 1. Recommendations and vaccination programs for universal varicella vaccination 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 & D2 MMRV between 11-23 m (4-week interval)
Finland	2017	National	D1 MMR+V 12 m D2 MMRV 6 y
Germany <sup>i</sup>	2004	National	D1 MMR+V 11-14 m D2 MMRV 15-23 m
Greece <sup>i</sup>	2006	National	D1 MMR+V 12/15 m D2 MMRV 4/6 y
Italy <sup>i</sup>	First regional recommendation (Sicily) in 2002	National	D1 MMR+V 13/15 m D2 MMRV 5/6 y
Latvia*	2008		D1 12-18 m
Luxembourg <sup>i</sup>	03/2009	National	D1 MMRV 12 m D2 MMRV 15-23 m
Spain <sup>i</sup>	First regional recommendation (Navarra) in 2006	National	Navarra D1 MMR+V 15 m D2MMR+V 3y Melilla D1 MMR 12 m & D2 4 y D1 V 15 m & D2 2y Ceuta D1 MMR 15 m & D2 3 y D1 V 18 m & D2 2 y
Cyprus	2010	National	D1 13-18m D2 4-6 y

\*all countries recommend a 2-dose regimen except Latvia which recommends a one-dose regimen

<sup>i</sup>UVV (universal varicella vaccination) is publicly funded

D1 - dose 1, D2 - dose 2, MMR - measles, mumps, and rubella combination vaccine, MMRV - measles, mumps, rubella, and varicella combination vaccine

Table 2. Summary of Impact of Varicella Vaccine in Europe

<b>Country</b>	<b>Burden</b>	<b>Herd immunity</b>	<b>Varicella age shift</b>	<b>HZ incidence</b>	<b>Vaccine Effectiveness</b>
<b>Germany</b>	All cases >50% reduction Hospitalization >70%	Indirect protection of <1 year old unvaccinated	Not observed	Increasing burden, secular trend?	All 86% dose 1 94% 2 doses
<b>Italy</b>			Secular trends not conclusive	No evidence	All 98% dose 1 Severe 99% (dose1)
<b>Greece</b>	Reduction of all cases Reduction of hospitalization and complications		Not observed (small cluster in 2012)	No increased risk in children	
<b>Spain</b>	Impact on total cases and hospitalization	No evidence	No evidence	Secular trends	87% after a single dose, 97% two doses