REVIEW 10.1111/1469-0691.12580

Varicella vaccination: a laboured take-off

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Abstract

Varicella vaccines are highly immunogenic, efficacious and safe in preventing varicella disease. The USA has been the first country recommending universal vaccination. In the European Union/European Economic Area countries, the use of varicella vaccine is heterogeneous, with some countries recommending universal vaccination in children at national or regional level, others only in high-risk groups and others having no recommendation at all. Uncertainties on the potential impact of varicella vaccination on the epidemiology of varicella and herpes zoster still exist. These uncertainties are the main reason behind the diverse vaccine recommendations. Surveillance systems and mathematical models could be useful to address these uncertainties. However, the lack of surveillance of varicella and herpes zoster in some countries, as well as the high variability of surveillance systems in the countries that have one, makes it difficult to assess the effect of the vaccine. On the other hand, mathematical models are based on assumptions and should be interpreted carefully. Continuous surveillance of varicella and herpes zoster is needed to identify any changes in the epidemiological presentation of the diseases. In any case, continuous surveillance will be needed to fully describe the impact of the programmes currently running and clarify some of the actual uncertainties in the near future. Additionally, increasing our understanding of the risk factors for development of herpes zoster is required.

Keywords: European union, vaccine recommendations, varicella, varicella surveillance, varicella vaccination
Article published online: 3 February 2014
Clin Microbiol Infect 2014; **20** (Suppl. 5): 86–91

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This article is based on the presentation 'Chickenpox vaccination: a laboured take off' given at the 2nd ESCMID Conference on The Impact of Vaccines on Public Health [1].

Varicella

Varicella is an acute infectious disease caused by the varicella zoster virus (VZV). Like other herpesviruses, VZV persists in the body after the primary infection as a latent infection. Primary infection with VZV results in varicella (chickenpox). Re-activation of latent infection results in herpes zoster (HZ; shingles).

The mode of transmission of varicella is mainly airborne. The disease is characterized by fever and a generalized rash, in varying stages of development and resolution. By adolescence, 90% of the population in Europe has had the disease. Although it is mostly mild in children, complications can occur, especially in older age groups, the fetus (congenital varicella syndrome), newborn infants (neonatal varicella), and immunocompromised patients [2].

Varicella Vaccines

The first varicella vaccine was developed in 1974 in Japan. It is still the only strain currently available for use in production of varicella vaccines. Several monovalent (only varicella) and combined (with measles, mumps and rubella, MMRV) varicella vaccines are currently authorized in Europe.

There is growing evidence indicating that monovalent and combined varicella vaccines are highly immunogenic, efficacious and safe in preventing varicella disease. Efficacy has been shown

to be around 70–90% against varicella disease and 95–100% against severe varicella [3]. Additionally, a two-dose vaccination regimen has proven to result in higher seroconversion rates and vaccine efficacy compared with a single dose administration [4].

The most common adverse reactions following varicella vaccine are local reactions, such as pain and erythema [3]; however, after vaccination with the combined vaccine (MMRV), a two-fold higher risk for febrile seizure after 5 to 12 days among children aged 12–23 months has been observed in post-licensure analysis [5,6]. This means one additional febrile seizure every 2300 children vaccinated with the MMRV vaccine. MMRV has the great advantage of providing four vaccines in one visit. Even though febrile seizures are not uncommon in young children and generally have an excellent prognosis [7], some require hospitalization and are distressing to parents. Some countries recommend using separate vaccines only for the first dose, as the MMRV as second dose is less likely to cause fever and rates of febrile seizure are lower in older children. However, the Advisory Committee on Immunization Practices (ACIP) in the USA does not express a preference for use of MMRV vaccine over separate injections of equivalent component vaccines (i.e. MMR vaccine and varicella vaccine) [7].

A WHO position paper on varicella vaccines [8] recommends that policymakers should consider varicella vaccination in countries where varicella is a relatively important public health and socio-economic problem (compared with other health priorities), where the vaccine is affordable, and where high (85–90%) and sustained vaccine coverage can be achieved (childhood immunization with lower coverage could theoretically shift the epidemiology of the disease and increase the number of severe cases in older children and adults). Additionally, the vaccine may be offered in any country to individual adolescents and adults without a history of varicella.

Experience in the USA

Since 2006, the US ACIP has recommended a routine two-dose varicella vaccination programme for children, with the first dose administered at 12–15 months of age and the second dose at age 4–6 years [4]. Additionally, vaccination of susceptible people who have close contact with persons at high risk for serious complications of varicella is recommended. The USA was the first country to introduce universal varicella vaccination. In fact, vaccination had started with a one dose schedule in 1996 [9], but the 85% effectiveness of one dose of vaccine had proved insufficient to prevent transmission, especially in high-contact settings such as schools, where small varicella outbreaks continued to occur.

The US varicella vaccination programme has dramatically reduced varicella incidence (by 90%) as well as related complications, hospitalizations and deaths.

Experience in the EU/EEA

Information regarding the status of the introduction of varicella vaccination in the European Union/European Economic Area (EU/EEA) countries is available from the Vaccine European New Integrated Collaboration Effort (VENICE) network and former European network for surveillance of vaccine preventable diseases (EUVAC.NET); both the VENICE network (in collaboration with the European Centre for Disease Prevention and Control (ECDC)) and the former EUVAC.NET performed a cross-sectional survey in 29 EU/EEA countries in 2010 [10,11].

Moreover, ECDC collects information on vaccination schedules in the EU/EEA countries with the help of ECDC national focal points [12]. The information is displayed, by country and by disease, at ECDC's website (http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx), with at least annual updates.

The majority of countries in the EU/EEA (22 out of 29) have some kind of recommendations for varicella vaccination [10] (Fig. 1).

Five countries (Cyprus, Germany, Greece, Latvia and Luxemburg) have a nationwide universal recommendation of varicella vaccine for children. In Italy and Spain a universal childhood recommendation of varicella vaccine is implemented only in some regions.

Seventeen countries (including the two with regional universal recommendation) recommend nationwide vaccination for susceptible teenagers (seven countries) and/or susceptible risk groups only (19 countries). There are seven countries with no specific recommendation for varicella vaccination.

Information on the year of introduction of vaccine recommendation, number of doses and age of varicella vaccination for countries or regions with universal vaccination are provided in Table 1. The first dose is indicated between 11 months and 2 years, depending on the country. For the countries with a two-dose schedule, the age of the second dose varies from 15 months to 6 years.

The data show that Germany, where the vaccine was introduced in 2004, is the European country with the largest experience using universal varicella vaccination.

Concerns Regarding Varicella Vaccination

Varicella vaccine has an excellent safety profile and high performance. All studies available from EU countries show,

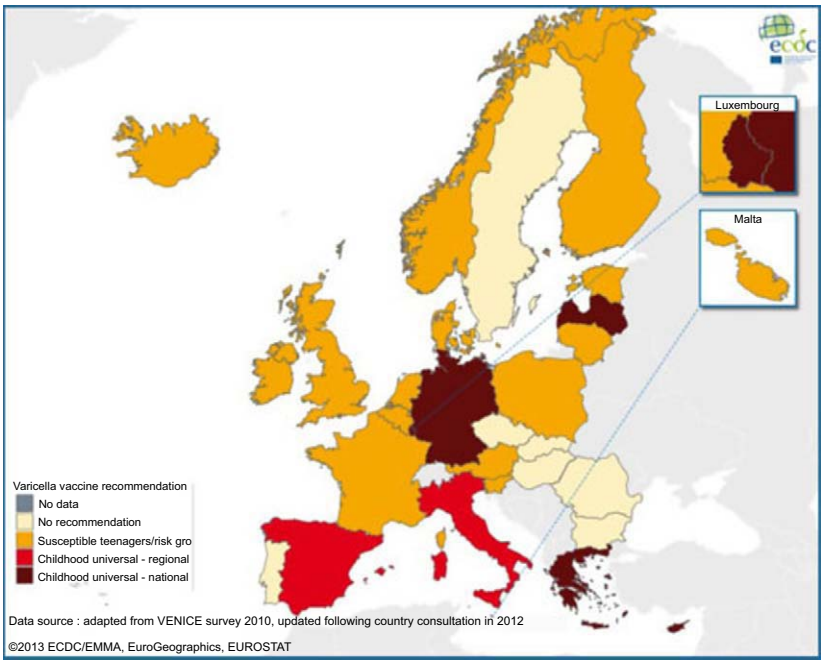

FIG. 1. Varicella vaccination recommendation in European Union/European Economic Area (EU/EEA) countries, 2012.

TABLE 1. Year of introduction, number of doses and age of varicella vaccination in European Union and European Economic Area/European Free Trade Association countries with childhood universal vaccination, 2012

	Year of introduction	First dose	Second dose
Germany	2004[a]	11–14 months	15–23 months
Latvia	2008	12–15 months	–
Greece	2006	12–15 months	4–6 years
Cyprus	2010	13–18 months	4–6 years
Luxemburg	2010	12 months	15–23 months
Italy			
Sicily	2003	2 years	–
Veneto	2005	15 months	3 years
Puglia	2010		
Toscana	2010		
Spain			
Madrid	2006	15 months	–
Navarra	2007	15 months	3 years
Ceuta	2009	18 months	24 months
Melilla	2009	15 months	24 months

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

similar to US studies, a dramatic decrease in the incidence of varicella and varicella complications after the introduction of vaccination into the routine schedule. So, why has there been a laboured take-off of varicella vaccination?

As mentioned at the start of this article, reactivation of latent infection of VZV results in HZ. Factors associated with VZV reactivation in HZ include mainly aging and immunosuppression [13]. However, the immunological mechanisms that control latency of VZV are not well understood. Cell-mediated immunity appears to play an important role in the host immune response to VZV [14], and development of HZ may occur as cell-mediated immunity declines with advancing age or other immune-suppressing factors [14–19].

Additionally, cell-mediated immunity may be boosted periodically by endogenous subclinical reactivation of latent virus or by re-exposure to exogenous virus from individuals suffering from varicella or HZ [20]; there are studies both supporting [21–24] and not supporting [25] this theory. Ogunjimi *et al.* [26] recently published a systematic review of the literature concluding that exogenous boosting for VZV seems to exist, but it remains unknown to what extent it affects HZ incidence.

Therefore, an increase in coverage of varicella vaccine, and the consequent decrease of wild-type virus circulation, could have a potential impact on the epidemiology of varicella and HZ. The uncertainties regarding these potential effects are the main reasons for the diverse current policies in the EU/EEA countries.

Indeed, as overall disease incidence declines due to vaccination, the VZV exposure risk decreases, leading to susceptible children aging into adolescence and adulthood. Accumulation of susceptible individuals may result in disease outbreaks later in life, when varicella is more likely to be severe. Also, in case of waning immunity, there could be susceptible populations at older ages. Additionally, if the exogenous boosting theory proves to be correct, low exposure to VZV could potentially lead to an increase in HZ

incidence, as a result of the reduction of immunological boosting caused by the varicella vaccination.

Epidemiological data from countries with experience on varicella vaccination have not, so far, shown a shift in the age at varicella infection, nor an increase in HZ. However, more years need to pass to fully understand the effects of the vaccine recommendations now in place.

Modelling Studies

To cover these uncertainties, several studies on mathematical modelling on varicella vaccination have been conducted. These studies use assumptions to predict what will happen in different scenarios. It is important to take into account that models are sensitive to the assumptions used, so these studies should be interpreted carefully.

In the case of varicella vaccination, data on breakthrough cases, long-term protection, importance of coverage level, and impact on HZ data mostly come from modelling studies.

Regarding the impact of varicella vaccination on varicella epidemiology, most models have predicted that varicella vaccine would produce a rapid and sharp decrease of varicella in the first decade after vaccine introduction, which is consistent with the available epidemiological data. If low coverage levels are attained or if a one-dose strategy is used, a post-honeymoon epidemic is likely to occur. A shift in the average age of infection (with an increase in the absolute case in adults) is expected if coverage is below 80%.

Regarding the impact of varicella vaccination on the epidemiology of HZ, most models have predicted an increase in the incidence of HZ in the medium term (30–75 years), followed by a decrease (assuming contact with VZV boosts HZ immunity).

Conversely, new models [27] have shown that an increase of HZ incidence is not expected to occur in all countries introducing varicella vaccination, but rather seems to depend on the presence or absence of factors that promote a strong intensity of boosting and so may (or may not) be heavily affected by changes in the circulation of the virus due to vaccination campaigns. These findings might provide an explanation for the opposed empirical evidence generated about the increases of HZ in sites where mass varicella vaccination is ongoing.

Countries with No Universal Recommendation

The Joint Committee on Vaccination and Immunization (JCVI) in the UK considered, between 2007 and 2009, the potential use of varicella and herpes zoster in vaccination programmes in the UK [28]. Data from a sentinel general practitioners network and seroprevalence studies have shown that in the UK most infections occur before the age of 14 years, and that there has been an age-related change during last 20 years towards children <5 years old, where disease is less severe. Following these data as well as other information available, a universal varicella vaccination for children was not recommended in the UK. Nevertheless, the JCVI will keep this recommendation under review in light of emerging data on the epidemiology of varicella and herpes zoster infections and the cost-effectiveness of vaccines against these infections.

In France, The 'Haut Conseil de Sante Publique' re-evaluated in 2007 the recommendations for a vaccine against varicella [29]. Following consideration of the US experience, epidemiological and modelling data, data available on vaccines and data on the potential acceptation of the vaccine in France, they decided not to recommend universal childhood vaccination. Nevertheless, a two-dose schedule is recommended in the country for susceptible adolescents (12–18 years) and adults in specific risk groups (women of childbearing age, candidates for organ transplantation, occupational risk groups and seronegative close contact of immunosuppressed individuals).

Surveillance Systems of Varicella and HZ in the EU/EEA

Surveillance systems for vaccine-preventable diseases are essential before a vaccine is implemented to estimate the burden of disease and to decide on the appropriate vaccination strategies. Additionally, post-introduction data are required to monitor vaccine programme performance. Surveillance systems could help to assess the impact of varicella vaccination on the epidemiology of varicella and HZ and could provide an answer to some of the uncertainties around the vaccine. Information regarding the surveillance systems of varicella vaccination existing in the EU/EEA countries is available from the VENICE and EUVAC.NET surveys [10,11].

Varicella surveillance is in place in 22 out of 29 countries participating in the surveys. The characteristics of these surveillance systems vary widely throughout the countries. Fundamentally, a standardized case definition for varicella at EU/EEA level does not exist, and countries use different definitions. In 18 countries reporting is mandatory and it includes all cases of varicella (comprehensive system), and in eight countries a sentinel system is in place. Data collected differ among countries, with some countries collecting all cases whereas others only collect cases with complications. Also,

data available are different: in some countries there is information available for each case whereas in others only aggregated information (total number) is available.

Regarding HZ surveillance, only 11 out of 29 countries have any system in place. There is clinician-based sentinel surveillance in six countries and other forms of surveillance in six countries.

Conclusions

Varicella vaccines are highly immunogenic, efficacious and safe in preventing varicella disease. However, uncertainties over the potential impact of varicella vaccination on the epidemiology of varicella and HZ still exist. These uncertainties are the main reason behind the heterogeneous use of varicella vaccine in the EU/EEA countries, with some countries recommending universal vaccination in children either nationwide or in some regions only, others only in high-risk groups and others having no recommendation at all.

The lack of surveillance of varicella and HZ in some countries, as well as the high variability of surveillance systems in those countries that have one, makes it difficult to assess the effect of the vaccine. Continuous surveillance of VZV and HZ is needed to identify any changes in the epidemiological presentation of the diseases. In any case, continuous surveillance will be needed to fully describe the impact of the programmes currently running and clarify some of the actual uncertainties in the near future. Additionally, increasing our understanding of the risk factors for development of HZ is required.

Transparency Declaration

Both authors declare that they have no financial conflicts of interest. The lead author (Paloma Carrillo Santisteve) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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