

## EDITORIAL

# VZV infection: epidemiology and prevention

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## Introduction

Varicella is an infectious disease caused by a virus (VZV), identified almost a century ago, belonging to herpesvirus family [1].

The disease mostly affects younger age classes. Although considered a mild disease, in some cases, especially in immunocompromised subjects, varicella can be severe, even fatal. The clinical course of the disease is longer in adults and more severe than in childhood [2]. VZV infection in susceptible pregnant woman, although rare, can cause severe forms both in the mother and in the newborn. A disabling congenital or neonatal varicella syndrome can affect the offspring born to a woman who contracts VZV during pregnancy [3].

During primary infection, VZV has the ability to become latent in the sensory-nerve ganglia and to cause, many years later, the reactivated form, herpes zoster [4].

The epidemiological relevance of varicella and the availability of a live, attenuated, safe and effective vaccine [5, 6], have prompted an ample international debate on the opportunity of extensive infant varicella vaccination.

Recently, a new high-potency, live, attenuated varicella zoster vaccine has demonstrated able to reduce morbidity and complications associated to zoster [7].

## General microbiological and epidemiological features

Varicella-Zoster virus (VZV) is an alphaherpesvirus, with a DNA genome, characterized by a lipoproteic envelope and a icosahedral capsid. The virus can spread by release of enveloped virions in the extra-cellular space or by cell to cell spread. The first case is typical of vesicular skin lesions and represents the lytic infection, while the latter is sustained by non-enveloped virions and is thought to be important during natural infection, contributing to the dissemination of viruses to the skin [8].

During primary infection, mainly during the exanthematic phase, VZV has the ability to become latent in the sensory-nerve ganglia. The latent phase is characterized by the expression of only a small subset of viral proteins; when lytic infection develops, herpes zoster occurs [8, 9].

Varicella is an airborne disease; the virus spreads from person to person via Flugge droplets or via direct contact with skin lesions of patients affected by varicella or zoster [10].

Man is the only reservoir of infection and varicella has a typical endemic-epidemic course. The disease mostly affects childhood. The period of incubation ranges between 14 and 16 days; this period could be longer (28 days) in subjects treated with specific immunoglobulins. The first period of infection involves various mucosal sites (nasopharynx, conjunctivae); subsequently the virus spreads to regional lymph nodes and after two viraemic phases causes the typical maculopapular-vesicular rash, characterized by several crops of vesicles containing large amounts of enveloped virus. In immunocompromised patients viral replication persists longer and the clinical feature of infection can be more severe and complicated with pneumonia, encephalitis, cerebellitis, etc. [11]. Patients with varicella and zoster are both infectious. Contagiousness begins 1-2 days before the onset of rash and lasts until the last crop of vesicles has crusted.

From the clinical point of view, varicella is considered a benign disease. However, complications, such as cutaneous bacterial superinfections, upper and lower respiratory tract infections, conjunctivitis, corneal infections and SNC involvement, are possible also in pediatric age [12-14]. The clinical course of infection acquired in adults is prolonged and more severe than in childhood [2]. The relation between frequency and severity of complications and older age of acquisition of infection is confirmed by the increased rate of hospitalization registered in adults [9]. The augmented rate of complicated forms of infections in adults is probably related to a lower cell-mediated immune response than in children.

In pregnancy VZV infection, even if rare, can have a severe impact both on mother and offspring [3]:

- severe VZV in the mother, particularly if infection has been acquired in the third trimester of pregnancy;
- disseminated VZV in newborn, when the mother develops the disease from 5 days before to 2 days after delivery;
- congenital syndrome, when the mother has acquired infection between the 8th and 20th week of pregnancy.

As mentioned before, reactivation of latent virus, years after primary infection, causes the clinical picture called zoster or shingles. Reactivation is directly related to a reduction of specific T-lymphocytes. During lifetime the risk of an episode of zoster is estimated equal to 10-30% and incidence increases sharply in older ages [15, 16]: 50% of people older than 85 yrs have at least one episode of zoster.

Clinically, zoster is characterized by a dermatomal

painful vesicular rash lasting, in the immunocompetent patient, 2-3 weeks. In a certain percentage of patients pain persists for several weeks or for months or years after disappearance of the rash. This chronic pain, called post-herpetic neuralgia (PHN), represents an important cause of stress and disability and significantly contributes to worsening the patients' quality of life [17].

Decay of the cell-mediated immune response and increasing age represent important risk factors for zoster; intrauterine exposure and VZV acquisition before 18 months of age are also related to an increased risk of zoster. No clear relation has turned out for other risk factors such as gender, stagionality, race, psychological stress, exposure to immunotoxic chemical substances, mechanical traumas and genetic susceptibility [18].

All updated studies confirm the impact of zoster on population in terms of morbidity, rate and length of hospitalization, worsening of the clinical conditions of patients affected by other pathologies. All these parameters increase significantly in older subjects [19].

## Immunological aspects

VZV natural infection induces a long lasting immune response against clinical disease; during primary infection the immune system is activated and produces first IgM and subsequently IgG. These latter seem to persist lifelong, even though some studies hypothesize that the persistence of immunity depends on both exogenous and endogenous boosters. However, naturally acquired immunity following VZV infection does not prevent virus latentization nor subsequent reactivation in zoster.

During natural infection there is an activation of both humoral and cellular branch of the immune system [10, 20, 21].

The absence of anti-VZV antibodies does not necessarily imply susceptibility, as cell-mediated response (CMI) can persist. About 20% of 55-65 years old people do not have specific CMI, even if they have a positive anamnesis for varicella and are anti-VZV positive. An episode of zoster elicits a reactivation of T-cell specific response. Nowadays, there is ample consensus on the link between low/absent cell-mediated specific immunity and incidence of zoster [22, 23].

## VZV and Zoster epidemiology in Italy

In Italy, varicella is subject to mandatory notification and is included in the 2<sup>nd</sup> class of notifiable infectious diseases [24]. All reported cases are recorded by Italy's National Census Bureau (ISTAT). Other databases exist for varicella, such as Italy's Paediatric Sentinel Surveillance System of Vaccine-Preventable Diseases (SPES) and the National Hospital Discharge Database (SDO). This latter was created in 1994 in order to collect information on all hospitalizations recorded in Italy [25]. For zoster, notification is not mandatory; thus no national-level data are available except for SDO records.

In our country, because of absence of extensive vaccinal intervention, varicella is an endemic-epidemic disease; virus spreading determines each year approximately 500,000 new cases, which correspond to a birth cohort [26].

The overall standardized annual incidence ranged from 164.4 to 244.2 per 100,000 population in the years 1991-2004. The disease mainly affected children (0-14 years); the analysis by geographic area showed that, although the trend in incidence was similar for the three areas, there was a clear north-south gradient, with the highest incidence consistently found for Northern Italy, followed by central and then southern Italy. The evaluation of SPES database has confirmed that varicella is a wide spread infectious disease and that the notification system greatly suffers from underreporting.

According to the National Hospital Discharge Database, in the period 2000-2003, there was an annual mean of 1,575 hospitalizations for varicella (1,521 hospitalizations and 54 day-hospital admissions). The mean duration of stay was 5.3 days.

A seroprevalence study, recently conducted, confirmed that in Italy VZV infection is predominantly a paediatric disease, and the results did not substantially differ from those of a study conducted using the same methods on samples collected in 1996-1997 [27]. The trend in seroprevalence was similar for males and females; it was also similar when comparing the three geographic areas. The mean geometric titer (GMT) showed progressive increase, indicating, as found in 1996-97, the existence of natural boosters deriving from the persistent circulation of the etiological agent. Nonetheless, it should be stressed that, for both genders, approximately 15% of adolescents and 9% of subjects in the 20-39 year age group are susceptible.

The sero-epidemiological profile in Italy is different from that in other European countries. As shown by other Authors [28-31], in Italy, the rate of susceptible subjects is at least nearly twice as high as the percentages in the other countries participating in the European Seroepidemiology Network (ESEN). This confirms that there are important differences in the age of disease acquisition, and it is consistent with the finding that, among the ESEN countries, Italy has the lowest reproduction number ( $R_0$ ) and force of infection. Moreover, in Italy, the high percentage of subjects who are susceptible in the 20-39 year age group indicates that there is a concrete risk for VZV infection for pregnant women.

For zoster, notification is not mandatory and data available come from studies conducted in different areas and with different methodologies. However, a retrospective observational study conducted at national level in 1996 involving Dermatologists, Geriatric Doctors and General Practitioners allowed to estimate that each year in Italy occur 200,000 cases of zoster and 42,000 cases of post-herpetic neuralgia in subjects older than 15 years [32]. In this study, 45.8% and 44.2% of cases involved respectively subjects older than 65 yrs and subjects still working. The mean duration of each case was 11-15 days and the overall rate of complications resulted 19.6%; PHN

was the most common complication. Antivirals were prescribed in almost all patients.

The National Hospital Discharge Database, even if affected by underestimation, permits to evaluate the impact of zoster in Italy. In the period 2000-2003, there was an annual mean of 5,250 hospitalizations (4,711 hospitalizations and 539 day-hospital admissions). The mean duration of stay was 8.3 days. Of the total hospital admissions for zoster, 62.1% were for subjects older than 65 years of age.

In the period 1992-2001, 301 deaths for zoster were reported; 88.7% of these occurred in subjects > 70 years, probably affected by other underlying pathologies.

## Preventive measures

In Italy, according to law [33], there are some preventive measures to be adopted against varicella. Considering the period of contagiousness, these are:

- isolation at home for at least 5 days since the appearance of the first crop of vesicles, avoiding contacts with susceptible subjects, especially pregnant women and newborns;
- in case of hospitalization, strict isolation taking into account the possibility of transmission of infection to susceptible immunocompromised subjects.

No restriction from school or other community attendance is required for household contacts and other contacts.

In case of hospitalization of a contact for other reasons, isolation should be provided for 10-21 days since the last contact with a varicella case (28 days in the case of administration of specific immunoglobulins).

Vaccination of subjects at high risk of complications due to VZV infection is indicated by Circular n° 8 of March 10<sup>th</sup>, 1992 [34]. This circular focuses attention on the severe clinical course of VZV infection in subjects affected by chronic renal failure, lymphoproliferative diseases, leukemia, and in candidate recipients of bone marrow, liver and renal transplant.

Varicella can be prevented by the administration of specific immunoglobulins within 72-96 hours of exposure; this kind of intervention is indicated in immunocompromised subjects, susceptible pregnant women and newborns from mother affected by the disease between 7 days before and 2 days after delivery.

## Vaccination

The development of a vaccine against varicella has represented a very important task, involving many Researchers and taking a lot of efforts, being a vaccine against an herpesvirus, able to cause latent infection. The live, attenuated vaccine was developed by Takahashi and Co-workers at the Biken Institute in Osaka, Japan, in the early '70s using the virus isolated from a 3 years old healthy child, called Oka [35]. The virus strain was attenuated with 11 passages at 34 °C in hu-

man embryonic lung fibroblasts, followed by 12 passages at 37 °C in guinea pig fibroblasts and 5 passages at 38 °C in human diploid fibroblasts (Wi-38).

Nowadays, all commercially available vaccines use the Oka strain of VZV; however, they differ for the number of passages in Wi-38, the viral amount in each dose, recipients and other aspects covered by trade mark.

The vaccines available in Italy are Varivax (MSD) and Varilrix (GSK); both products are safe and effective [10] and are administered in one dose in children up to 12 years and in 2 doses (4-8 weeks apart) in subjects 13 years or older.

In terms of efficacy, both vaccines induce high seroconversion rates; 87% and 97% of healthy children reach a level of antibodies considered protective after 1 and 2 doses, respectively.

The vaccine should be administered subcutaneously and can be given simultaneously with other vaccines (e.g. Measles-Mumps-Rubella [MMR]); if co-administration is not possible, it is necessary to separate the administration of 2 vaccines > 4-6 weeks. The use of blood or blood products 5 months before or 3 weeks after vaccine administration can reduce its efficacy.

The use of several million doses worldwide has demonstrated the safety of the commercially available vaccines; local and general side effects could be possible, but they are usually moderate, self-limiting without sequelae.

Vaccine virus transmission is possible but extremely rare and is related to a rash following administration.

Contraindications to the use of VZV vaccine are the same adopted for all vaccine containing live, attenuated virus; besides, VZV vaccination should be avoided in pregnancy, in case of known allergy to vaccine components or of any reaction to previous doses. In acute severe illness, such as untreated active tuberculosis or recent administration of blood, plasma or immunoglobulins vaccination can be postponed until recovery or possible interference ends.

Clinical trials with VZV vaccine in bone marrow transplants, in patients waiting for renal transplant, leukemic children in remission, HIV-positive children and children with solid tumors before chemotherapy have been conducted. In most cases 1 or 2 doses have induced a high degree of protection with mild side effects. From the practical point of view, nowadays VZV vaccine administration is allowed in leukemic children in remission and in HIV-positive subjects not severely immunocompromised [36].

VZV vaccine is effective in preventing illness or at least modifying disease severity if administered as post-exposure prophylaxis. This latter should be adopted within 3-5 days after exposure/contagion and it is indicated for subjects at high risk of complications in case of varicella.

Since 2005 in the USA a tetravalent combined vaccine MMRV (measles-mumps-rubella-varicella) (Proquad, Merck) has been licensed and is commercially available for use in children aged 12 months to 12 years; more recently this product has been licensed and commercial-

ized in Europe. This vaccine contains a higher dose of live, attenuated VZV virus in respect to the monocomponent vaccine; it induces seroconversion rates > 98% after 2 doses and has an excellent safety and efficacy profile [37, 38].

Another quadrivalent combined vaccine (Priorix-Tetra, GSK) has recently been licensed in Germany and Australia; safety, tolerability and efficacy of this product are excellent and not significantly different from what observed with the monocomponent vaccine already commercially available [39].

## VZV vaccine: controversies and scientific debate

The main point is represented by the notification of varicella cases in vaccinated subjects (breakthrough infection) and of epidemic outbreaks in communities with a high vaccination coverage rate. These cases seem to show a level of vaccine effectiveness lower than expected on the basis of clinical trials previously conducted. Breakthrough infection is defined as skin lesions, generally 10-20, diagnosed as chickenpox, occurring at least 42 days after vaccination and caused by wild-type VZV. A breakthrough infection can be evaluated as a primary (no-take) or secondary (immune response decreases over time) vaccine failure. Noteworthy, each case of breakthrough infection is infectious and represents a risk of virus transmission in a community.

The hypothesis of a long duration of immune protection following VZV vaccination has been based on the Japanese data, showing that antibodies induced by vaccination were still detectable 20 yrs after immunization. It is important to note that this persistence has to be related to the ample possibility of natural boosters, being the vaccine coverage rate 20%.

Some Authors have verified that protective efficacy lowers in particular if vaccine has been administered before 15 months of age. For this reason, in order to avoid interference due to maternal antibodies it seems appropriate to vaccinate children > 15 months of age and to adopt a second dose of vaccine [5, 10, 40]. Even if the causes of breakthrough varicella need to be further elucidated, the administration of a second dose of vaccine seems to have the potential to reduce primary and secondary vaccine failure. For these reasons, recently in the USA the Advisory Committee on immunization practices (ACIP) has adopted new recommendations regarding the use of live, attenuated varicella vaccines, implementing a routine 2-dose varicella vaccination program for children, with the first dose administered at 12-15 months and the second dose at age 4-6 years [36].

Another extremely interesting point that needs further studies is the possibility that immune response induced by vaccines containing Oka strain (Asian clade) could result less effective in areas, such as the USA, where different strains are circulating (European clade).

Finally, some Authors using mathematical models predict an increase of the incidence of herpes zoster

following the first few decades of extensive infant varicella vaccination [41, 42]. This fact could happen in non-vaccinated people as the consequence of the reduced spreading of the wild-type VZV, to the loss of exogenous boosting from contacts with chickenpox cases and then to the waning of CMI response. Updated researches conducted in USA, where widespread infant vaccination has been adopted almost ten years ago, have not confirmed this hypothesis; up to now no changes in the trend of zoster have been registered at national level following the increased varicella vaccination coverage rate [43]. In two cases, an augmented zoster incidence has been registered but has been related to an increased use of oral steroids or to a higher rate of immunocompromised subjects [44, 45].

## Prospectives of vaccination against herpes zoster

Several international researches have clearly demonstrated the epidemiological impact of zoster, its complications and related costs. Furthermore, there are no satisfactory treatment options for zoster complications and this implies additional costs and a bad quality of life for patients [46].

All these reasons have prompted preventive intervention against zoster and, along with the development of the varicella vaccine, some Researchers have evaluated the possibility to stimulate CMI response in order to reduce the incidence of zoster and its complications. During the last ten years it has been demonstrated that this target can be achieved using high-potency, live, attenuated VZV vaccine in elderly immunocompetent patients [47, 48].

Recently a double blinded clinical trial has been conducted in USA enrolling adults > 60 years of age. The subjects were treated with placebo or "zoster vaccine" (Oka/Merck) with a median potency of 24600 PFU, that means 14 times greater than varicella pediatric formulation [49].

In the period September 2001-April 2004, 38,546 immunocompetent subjects, with positive anamnesis for varicella or residing in the USA for at least 30 years, have been enrolled and followed up. Safety and efficacy of the "zoster vaccine" have been investigated as well as its impact on the burden of illness, incidence of zoster and PHN.

The new vaccine turned out to be safe; low rates of severe adverse events, systemic adverse events and hospitalizations have been registered. Local reactions were usually mild and transient. The vaccine did not cause cases of zoster.

The impact of vaccination on the burden of disease, incidence of zoster and PHN was equal to 61.1%, 51.3% and 66.5%, respectively.

This means that the new vaccine, increasing the CMI response, has a booster effect and represents a new option of preventive intervention against zoster and its complications [50, 51].



Noteworthy, this target is achievable only using a high-potency vaccine and up to now there are no data on the use of pediatric formulation in order to intervene against zoster and/or PHN in adults and elderly.

The vaccine, commercially available as Zostavax (MSD), has been licensed by FDA and in the USA there is the provisional recommendation for its use in a single dose in subjects  $\geq 60$  years.

At the moment no data are available on what could be the impact of such vaccine in relation to the age of patients treated and to the coverage rate achieved, and to what could be the best strategy of intervention. Possible options could be to intervene in subjects  $> 60$  years or  $> 65$  years, considering the already existing recommendations for flu and pneumococcal vaccinations in elderly and that the clinical trial conducted in USA showed the best results in subjects 60-69 years old.

However, there are no data on co-administration of the "zoster vaccine" with flu and pneumococcal vaccines, duration of the protection, opportunity of subsequent boosters and impact in terms of costs of the different options.

## Options of intervention

The epidemiological importance of varicella and zoster and the availability of a live, attenuated, safe and effective vaccine [5, 6] has prompted an ample international debate on the opportunity of an extensive vaccine intervention.

At European level, European Working Group on Varicella (EuroVar) has recently recommended routine varicella vaccination in healthy children 12-18 months and in all susceptible children before 13 years of age, catch-up immunization of older children and adults anamnesticly negative for the disease and at high risk of transmission and exposure or of complications.

This kind of intervention is recommended only for countries able to rapidly achieve and maintain a high coverage rate [52], in order to avoid perverse effects as already happened for Measles, Mumps and Rubella [53].

Before evaluating the different options of intervention against varicella, it is necessary to have complete and updated epidemiological data, the acquisition of which entails not only performing seroepidemiological investigations but also creating or implementing passive or active surveillance systems for varicella and zoster. Although on this point there is ample consensus, it is well known that not all the countries where extensive vaccination campaigns are starting or planned have adequate surveillance systems [54].

With regard to the vaccination options, mass vaccination in infancy (12-18 months of age) would substantially decrease the spread of the disease, have an impact on costs and would protect subjects at high risk of complications. The achievement of these targets implies a high vaccine coverage rate in order to avoid an increase in the mean age of acquisition of the infection and thus in the risk of complications. For these reasons, the vaccine intervention should be applied to children 12-18 months of age and in all susceptible subjects before 13 years [52]. In addition, a second dose should be adopted in order to guarantee the catch up of non responders to the first dose and to reduce the secondary vaccine failure [36, 40].

The immunization of susceptible adolescents and adults would represent an alternative option. This type of intervention would have a limited impact on the epidemiology of the infection, but it would contribute to decrease the incidence among persons at greatest risk of complications.

There is a theoretical negative impact of mass vaccination in terms of increasing the incidence of zoster, given that exposure to VZV boosts natural immunity [41]. This risk needs to be carefully considered; however, data currently available do not support this hypothesis [43]. Moreover, the possibility of using a vaccine with a high antigen titer for preventing zoster in adults is being considered [51].

In Italy, we are still in a pre-vaccine era; some Regions (Sicilia, Veneto, Puglia) have started or planned universal vaccination, others (Liguria, Piemonte, Valle d'Aosta, Emilia Romagna, Toscana, Basilicata, Campania, Lazio) have decided to immunize susceptible adolescents, while others (Lombardia, Trentino Alto Adige, Marche, Abruzzo, Umbria, Molise, Calabria, Sardegna) have not decided on any type of intervention.

Italy's 2005-2007 National Vaccination Plan [55] recommends vaccinating persons at high risk of complications, susceptible adolescents, healthcare workers, and the staff of day-care centres and schools with small children. Mass vaccination is only recommended in regions where a vaccination coverage of greater than 80% for MMR can be achieved. A cluster sampling survey conducted in 2003 revealed a national MMR vaccination coverage of 77%, in children aged 13-24 months of age [56] and routine coverage data provided by Regions to the Italian Ministry of Health in 2004 showed an MMR vaccination coverage of 85.5%. It is therefore possible that in a near future the conditions necessary for implementing a mass vaccination campaign will exist and that the large-scale availability of MMRV tetravalent vaccines will facilitate this strategy of intervention.

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