0021-7557/06/82-03-Suppl/S101
Jornal de Pediatria

doi:10.2223/JPED.1496

REVIEW ARTICLE

Varicella vaccines and measles, mumps, rubella, and varicella vaccine

Lucia Ferro Bricks,[1] Helena Keico Sato,[2] Gabriel Wolf Oselka[3]

Abstract

Objectives: To present an up-to-date review of studies investigating the efficacy, adverse events and vaccination regimens of the varicella vaccine and the new presentation combined with the vaccine for measles, mumps and rubella.

Sources of data: Bibliographic review of the MEDLINE and LILACS databases covering the period 1999 to 2006.

Summary of the findings: The varicella vaccine protects 70 to 90% of immunized children against any form of varicella zoster infection, but the efficacy against severe forms is higher (95 to 98%). This is a well-tolerated vaccine that causes few reactions. Since the vaccine was licensed, there have been three confirmed cases of transmission of the vaccine virus by domestic contacts to previously healthy people, who went on to develop mild disease. Despite evidence that the protection offered by this vaccine can wane over a number of years, it is not yet possible to state that a second dose is warranted, bearing in mind exposure to wild virus. After universal vaccination the chances of natural stimulation should drop and it is very probable that booster doses will become necessary. A measles, mumps, rubella, and varicella vaccine has recently been licensed that combines vaccines for measles, mumps, rubella and varicella in a single product with high rates of seroconversion.

Conclusions: The Brazilian Society of Pediatrics recommends the varicella vaccine for children from 1 year on. We hope that the measles, mumps, rubella, and varicella vaccine will soon be available in Brazil, since combined vaccines facilitate wider vaccination coverage.

J Pediatr (Rio J). 2006;82(3 Suppl):S101-8: Varicella, adverse events, efficacy, vaccination schedule, measles, mumps, rubella, and varicella vaccine.

Introduction

Chickenpox is caused by the varicella-zoster virus (VZV), which only infects humans and some higher primates. Acquisition of the disease depends on age, immune status, vaccination status and exposure type. Transmission is through intimate contact with sufferers during a period from 2 days before until 5 days after the appearance of vesicles. Clinical manifestations surface 10 to 21 days after contact and in more than 80% of cases include fever. Exanthema is absent in only 6% of affected individuals, the remainder exhibit cutaneous lesions that appear in clusters and progress rapidly from macules, through papules and vesicles to crusts. Normally, 5 to 6 days after the onset of exanthema, all lesions have reached the crusting phase. In the absence of secondary infection, varicella does not scar. In primary cases the number of cutaneous lesions is lower than in secondary cases (250 vs. 500, on average) and, generally, the disease is milder. Mortality is low (6.7/100,000), but lethality varies with age and immune status, being higher in groups at risk of complications (Table 1).[1-4]

The most common complications are secondary bacterial infections of the mucosa, skin, soft tissues and upper and lower airways, which occur in more than 5% of children. More severe complications, such as pneumonia and encephalitis, are rarer, although more severe; they occur in greater proportion among certain risk groups (Table 1), but in absolute numbers they primarily affect previously healthy children. Reinfection by VZV appears to be rare in immunocompetent people.[1-4]

1. Professora Doutora, Departamento de Pediatria, Faculdade de Medicina da Universidade de São Paulo (FMUSP), São Paulo, SP, Brasil. Médica assistente, Instituto da Criança, Hospital das Clínicas da FMUSP, São Paulo, SP, Brasil.
2. Diretora técnica, Divisão de Imunização, Centro de Vigilância Epidemiológica Prof. Alexandre Vranjac, Secretaria de Estado da Saúde de São Paulo, São Paulo, SP, Brasil. Doutora, Departamento de Pediatria, FMUSP, São Paulo, SP, Brasil.
3. Professor associado, Departamento de Pediatria, FMUSP, São Paulo, SP, Brasil.

Suggested citation: Bricks LF, Sato HK, Oselka GW. Varicella vaccines and measles, mumps, rubella, and varicella vaccine. J Pediatr (Rio J). 2006;82(3 Suppl):S101-8.

Table 1 - Risk groups for varicella complications

Risk group	Comments
– People with congenital or acquired immunodeficiency, such as HIV carriers, those on high dose corticosteroids for long periods (≥ 2 mg/kg/day of prednisone or equivalent, for more than 14 days); patients with malignant neoplasms; undergoing bone marrow or solid organ transplantation or subjected to chemotherapy or radiotherapy	– The use of inhaled corticoid, in low doses, intraarticularly or for short periods of time (< 14 days) does not increase the risk of complications, but severe cases occur among children given oral corticosteroid. It is recommended that in varicella cases this medication be suspended whenever possible
– Pregnant women	– 10 to 20% have pneumonia, with lethality of up to 40%; increased risk of premature delivery and miscarriage. During the first 16 weeks, 0.4 to 2% of fetuses will develop congenital varicella syndrome
– Babies whose mothers presented varicella 5 days before or 2 days after giving birth	– Increased risk of complications and of zoster
– Premature infants with birth weight below 1,000 g or gestation < 28 weeks exposed to varicella during the neonatal period	– Effective transmission of IgG from mother to baby only takes place after six months' pregnancy
– Children under 1 year old	– Increased risk of complications and zoster
– Adult adolescents	– Lethality in children is 1-2 per 100,000 and, in adults it reaches 25/100,000
– Secondary cases at home or day care or wards	– Increased number of lesions and chances of complications

Varicella-zoster virus remains in the organism in a latent state after the primary infection, and its reactivation leads to the onset of zoster, manifested by lesions similar to those observed with varicella, but more localized, following the path of one or more nerves. The incidence of zoster in early childhood is low (20 to 60 cases/100,000 people/year), but increases with age and with conditions associated with immunodepression, such as leukemia, transplantation and HIV infection.[1-4]

The majority of varicella cases occur in children. Seroepidemiological survey studies undertaken in Brazil revealed that almost half of the children tested had already been infected by 5 years of age. While there are major regional variations, children who live in crowded conditions or are looked after away from home contract the infection earlier and exhibit higher rates of complications.[4-8]

Varicella cases occur all year round, but in temperate climates the majority of disease outbreaks are recorded during the end of winter and start of spring.[1-4]

Varicella vaccines

Varicella vaccines contain live attenuated viruses, generally derived from the Oka strain, are formulated with varying numbers of VZV plaque forming units (PFU) and should be administered subcutaneously. The VZV is very sensitive to light and temperature variations, therefore vaccines should be kept at 2 to 8 °C protected from light (Table 2).

Table 2 - Varicella vaccines marketed in Brazil

Trade name	Producing laboratory
Varivax®	MerckSharpDohme
Varilrix®	GlaxoSmithKline
Varicela Biken®	SanofiPasteur

The currently recommended vaccination schedule is a single dose for children aged between 12 months and 13 years and two doses, with a minimum interval of 4 weeks, for people older than 13 years of age with negative history for the disease. One of the manufacturing laboratories also recommends a single dose for adolescents (SanofiPasteur®).[1-5]

Immunogenicity

Antibody production is related to the number of PFU in the vaccines, and also to age and immune status; however, even using the most potent vaccines, antibody production is many times weaker than after natural infections.[1-3]

More than 95% of previously healthy children aged between 12 months and 12 years exhibit adequate seroconversion after a single dose of the vaccine.[1-3] In adolescents, adults and the immunodepressed, post-vaccination seroconversion rates are lower and antibody titers decrease more quickly; therefore these individuals should be given two doses of the varicella vaccine, with a 4 to 8 week interval.[1-5,9-21]

There is no interference in immunoresponse to the varicella vaccine when it is administered simultaneously with other vaccines recommended for children; however, when the varicella vaccine is administered less than 1 month after the measles, mumps and rubella vaccine (MMR), reduced seroconversion rates are observed in response to the varicella virus.[1-3,9-21]

Adverse events

The most common adverse events are: pain, erythema and edema at the site of vaccine administration (15 to 25%), generally mild; fever (14%) and mild exanthema (4%). Exanthema can appear 1 to 3 weeks after vaccination, and may be in the site of administration or in other sites. The number of vesicles after vaccination is generally low, less than 10.[1-3] When the number of lesions after vaccination is greater than 30, a wild virus infection should be suspected, especially when these appear within the 2 first weeks of vaccination.[22]

Other adverse events after vaccination are very rare. A survey of adverse events associated with the vaccine after more than 16 million doses had been administered in the USA revealed that the vaccine is very safe. Although 19 cases of encephalitis and 24 of ataxia were recorded after vaccination, in none of these was infection by the Oka strain confirmed; in contrast, in two of these cases the wild virus was identified. None of the 14 deaths notified after vaccination was confirmed as being associated with the Oka strain and two were caused by wild viruses.[22]

Anaphylactic reactions after vaccination are rare and are generally associated with the gelatin used as a stabilizer in the vaccine.[1-4,22]

The vaccine virus is rarely isolated from healthy vaccinated people, since the majority do not exhibit cutaneous lesions and the risk of viral dissemination is directly associated with the presence of these lesions. Children with leukemia exhibit an increased chance of developing cutaneous lesions after vaccination; but, even under these circumstances the risk of transmission to susceptible contacts is, at most, 17%, much lower than the risk associated with contact with people infected by the wild virus (> 80%).[1-4,18,19]

After the varicella vaccine was licensed in the USA, just three cases were confirmed of transmission of the vaccine virus from previously healthy people to domestic contacts, and, in all cases, the contacts developed mild disease, with low numbers of lesions.[22]

The majority of reported cases of possible transmission of the vaccine virus were associated with infection by the wild virus. Comparing the low numbers of reports of vaccine virus transmission to non-immune contacts with the number of people vaccinated, this event appears to be extremely rare.[1-4,22]

There is a direct relation between the number of cutaneous lesions and dissemination of the vaccine virus. In all cases of vaccine virus transmission, contacts had mild disease, without fever, and with a low number of cutaneous lesions.[1-4,19] Despite the low risk of transmitting the vaccine virus, it is recommended that vaccinated children who develop cutaneous exanthema after vaccination avoid intimate contact with high-risk groups.[1-4] In the USA, after 30 million doses of the vaccine had been distributed, between 1999 and 2002, just three cases of vaccine virus transmission were detected with evidence of post-vaccination exanthema in all of them.[2]

Efficacy

It is estimated that the vaccine offers 70 to 90% protection against infection and 95 to 98% protection against severe forms.[1-3,9-15]

In a controlled study in which 2,000 children aged 1 to 12 years were randomized to receive one or two doses of the vaccine (Oka/Merck®), protection observed 42 days after vaccination was 94.4% for a single dose and 98.3% for two doses administered with a 3 month interval.

Some of the children who exhibited seroconversion presented mild cases of varicella during monitoring, known as modified varicella-like syndrome (MVLS). While the risk of presenting MVLS was 3.3 times greater in the group given a single dose of the vaccine, the difference between the groups was small (7.7% for the single dose and 2.2% for the group given two doses). All cases of secondary vaccine failure were mild and caused few lesions.

In one study, in which the Oka/Merck® vaccine was given to 603 children aged 12 months to 6 years, concurrently or not with the MMRII® vaccine, seroconversion rates were 99.5% (simultaneous vaccination) and 100% (6 week interval between varicella vaccine and MMRII®) and antibodies persisted for 6 years of follow-up in 98 to 100%. For both groups, effectiveness over 5 years was approximately 90%.[10]

Studies undertaken with the Oka/GSK® vaccine have also demonstrated excellent rates of post-vaccination seroconversion (> 98%); some of the children in this study were given the vaccine before reaching 1 year of age, without any increase in incidence or severity of post-vaccination adverse events.[13-15]

The principal factors associated with primary and secondary vaccination failure are listed in Table 3.[9-22]

Table 3 - Risk factors for primary and secondary vaccination failure

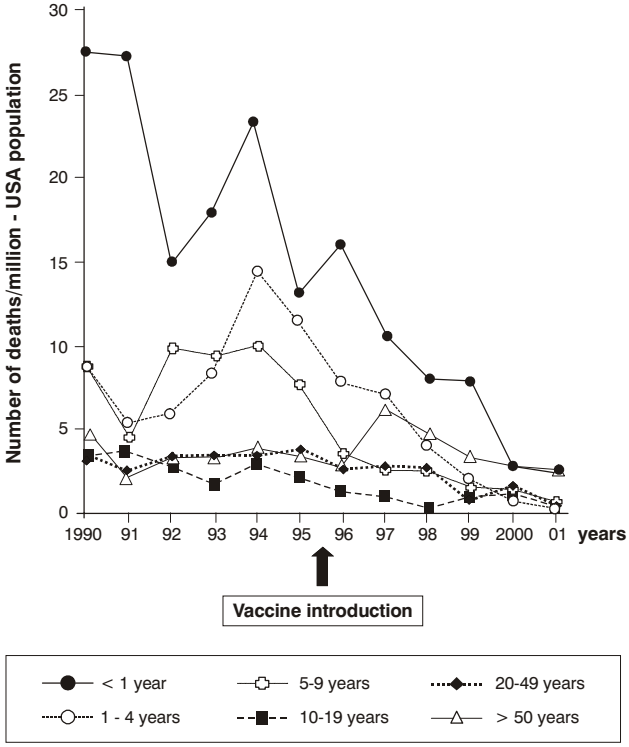
– Vaccination of very young children (< 15 or 18 months)
– Interval of less than 28 days between administration of the varicella vaccine and of MMR vaccine (measles, mumps and rubella)
– Time since vaccination (> 5 years)
– Use of oral corticosteroid after vaccination
– Domestic exposure to varicella
– Eczema

The probability of a vaccinated individual suffering secondary vaccination failure is inversely proportional to the antibody titers 6 weeks after vaccination,[13-15] but almost all of those children who had secondary vaccination failure exhibited low severity varicella episodes, with few cutaneous lesions, the majority papules.[9-22] It is rare for vaccinated children to present vesicles; since the number of vesicles is directly related to transmission of the disease, circulation of VZV is reduced in communities with high levels of vaccination coverage.[23-25]

Varicella outbreaks recorded at day care centers have led to speculation that there may be a need for a second dose of the vaccine.[22,26-28] Nevertheless, in many of these situations, cases occurred among children without confirmed vaccination and, furthermore, the secondary failure cases were mild. The issue of a second dose or not should take account of costs, risks and benefits, and also of the acceptance of yet another injected vaccine for children.

Despite evidence that the protection offered by the varicella vaccine may diminish as the years pass, it is not yet possible to state that a second dose of the vaccine should be recommended for previously healthy children, taking account of the fact that exposure to the virus in the wild can stimulate humoral and cellular immune memory, while full vaccination coverage does not exist. With universal vaccination, the reduced incidence of the disease should reduce the chances of natural immune memory stimulus, making booster doses necessary to maintain antibody titers at protective levels. Since the administration of a second vaccine dose to adults and children does not result in an increased number of adverse effects and can reduce rates of primary and secondary failures, it is very probable that, after the combined measles, mumps, rubella and varicella vaccine is licensed, it will be recommended in a two-dose regime.

The experience of the USA, where the varicella vaccine has been in widespread use for more than 10 years, in a single dose regimen, demonstrated that mass vaccination led to a significant reduction in the number of cases of disease, hospitalizations, number of medical consultations and deaths.[29-31] From the introduction of the vaccine (1995) until 2002, an 88% reduction in hospitalizations was verified, a 59% drop in medical consultations for varicella was observed and, during the same period, direct medical costs (hospitalizations and consultations) were reduced by 74%.[30] The impact of vaccination was evident not only in the groups targeted for vaccination, but in the general population, including those under 1 year old, clearly demonstrating that mass vaccination leads to herd immunity (Figure 1).[31]



Source: Nguyen et al.[31]

Figure 1 - Number of deaths associated with varicella per million North-Americans, by age group, 1990 to 2001

Post exposure vaccination

Administration of the vaccine within 96 hours of exposure can offer protection or attenuate the disease.[32]

Protection against herpes-zoster (HZ)

The incidence of zoster in healthy children is so low that, in order to discover the impact of routine vaccination on HZ incidence, it will be necessary to follow-up thousands of individuals for many years.[1-4] Studies undertaken in the USA after the varicella vaccine had been introduced reported some cases of HZ, but it is very difficult to isolate the virus from lesions, and in some of the HZ that occurred after immunization, the virus isolated was a wild form. In the rare cases of zoster that occurred in vaccinated individuals, the disease was milder, with few lesions and resolution was faster than in those infected by the wild virus. There are reports that vaccination of schoolchildren reduces the incidence of zoster by three times, and everything indicates that vaccination should be capable of reducing the risk of zoster.[1-3,33,34]

Two recently published studies that analyzed the impact of vaccination for varicella on the incidence of HZ in the USA reported different results.[33,34] In both studies a significant reduction was observed in the number of cases of varicella in all study groups. However, in the first study[33] the rate of HZ was stable, whereas in the second there was a discrete increase in the number of reports of HZ.[34] Since zoster notification rates are variable, further studies are still needed to evaluate whether the reduction in varicella cases may lead to an increase in zoster.

A vaccine for HZ to be used with the elderly, produced by the Merck® laboratory, was tested in a randomized, placebo-controlled manner with 38,546 people over 60 years. In the vaccinated group, the incidence of HZ was 51% below that for the placebo group. Furthermore, the incidence of postherpetic neuralgia in the vaccinated group was 61% lower than in the control group. Once licensed, this new vaccine should be recommended to reduce the incidence and morbidity associated with zoster in the elderly.[35]

Contraindications and precautions

The varicella vaccine contains live attenuated viruses and for that reason is contraindicated in the following situations.

General illness, with or without fever

Postpone vaccination so that possible adverse effects of vaccination will not be confused with symptoms from the underlying disease.

Congenital or acquired immunodeficiency

People with cell-based immunodeficiency should not be vaccinated, but some immunocompromised groups can be vaccinated on the public health system at the Special Immunobiology Referral Centers (CRIE – Centros de Referência para Imunobiológicos Especiais). Table 4 lists the vaccination criteria for the CRIE. While the varicella vaccine is recommended for certain immunocompromised groups, data on efficacy in these groups are scarce. In general, protection levels are lower than in previously healthy children. The vaccine is therefore recommended in a two-dose regimen, even for children aged 1 to 13 years.[1,16-17]

Table 4 - Recommendations for varicella vaccination at CRIE, 2005

1. Patients with acute lymphoblastic leukemia or solid tumors under the following conditions:
   – disease in remission for more than 1 year
   – off chemotherapy
   – white blood cell count over 700/mm^3
   – platelets over 100,000/mm^3
2. Asymptomatic or oligosymptomatic HIV carriers
   – white blood cell count over 15% and CD4+ > 25%
3. People and family in contact with the immunodepressed
4. Candidates for solid organ transplantation
5. Bone marrow transplantation patients
   – 2 years after transplantation, if off chemotherapy for at least 1 year
6. People admitted to wards for varicella
7. Severe dermatopathy sufferers
8. Chronic acetylsalicylic acid users
9. Patients with anatomic or functional asplenia
10. Patients with trisomies
11. Health professionals

Susceptible people older than 1 year and with negative history of varicella-zoster, with no need for laboratory confirmation.

Pregnancy

While there have not been any reported cases of congenital varicella associated with vaccination, the effects that the attenuated viruses have on fetuses are not yet known and pregnant women should not be vaccinated. It is recommended that, after puberty, women avoid conception for at least 1 month after vaccination. The presence of pregnant women in the home of vaccinated individuals does not constitute a contraindication for vaccination of non-immune individuals, because of the low possibility of transmission of the vaccine virus. If the vaccinated person develops exanthema, however, contact with pregnant women should be avoided.

Anaphylactic allergic reaction to gelatin or neomycin

Whenever there is a history of anaphylactic reaction to a previous vaccine dose (urticaria, bronchospasm, edema of the glottis, shock), a second dose is contraindicated. The vaccine contains traces of neomycin and gelatin; however, the majority of reactions to neomycin occur later and are not anaphylactic (contact dermatitis) and do not constitute contraindications to vaccination.

Precautions

Individuals who have contact with immunodeficient people, pregnant women or newborn infants

Vaccinated people who present post-vaccination exanthema should avoid contact with at-risk groups, despite the fact that the risk of transmission of the vaccine virus is very low. If inadvertent contact between people presenting post-vaccination exanthema and immunocompromised people takes place, specific immunoglobulin (VZIG) is not recommended since the risk of transmission of the disease is low.

Individuals given blood, plasma or immunoglobulin

It is not yet known whether these products interfere with seroconversion after varicella vaccination. Nevertheless, taking account of the fact that there is a reduction in the response to other vaccines using live viruses (measles and rubella), for 3 to 11 months, the American Academy of Pediatrics recommends waiting 5 months before administering the varicella vaccine (with the exception of concentrated red blood cells).[3] Whenever possible the administration of blood, plasma, immunoglobulins and VZIG should be avoided for at least 3 weeks after vaccination and, if this does not prove possible, it is recommended that immunity be tested after 6 months or that patients be revaccinated after 5 months.

Salicylates

Due to the association between Reye syndrome, salicylates and varicella, it is recommended that salicylate use be avoided for 6 weeks after vaccination even though to date no cases of Reye syndrome associated with the vaccine have been reported. It is not known whether or not there is a link between other non-hormonal anti-inflammatories and Reye syndrome or whether they should be avoided after vaccination.

Administration simultaneously with other vaccines

Several studies have demonstrated that administration of varicella vaccine simultaneously with other vaccines used on the basic schedule is as safe and effective as administering the vaccines with a 6-week interval. In contrast, if the varicella vaccine is given less than 28 days after the MMR vaccine, there is immunoresponse interference, with reduced varicella seroconversion. Therefore, when the measles, mumps and rubella vaccine cannot be given on the same day as the varicella vaccine, a minimum interval of 28 days should be respected.[1-4]

Measles, mumps, rubella, and varicella vaccine (MMRV)

Quadrivalent vaccines for measles, mumps, rubella and varicella (generally referred to as MMRV) have been in research for many years. Until recently, however, the varicella component in these vaccines offered unsatisfactory immunogenicity, which barred licensure.

In 2005, however, two quadrivalent vaccines, produced by MerckSharpDohme® (MSD) and GlaxoSmithKline® (GSK) were licensed in the USA and Australia, respectively. Both vaccines were licensed on the basis of the immunogenic equivalence of antigenic components, rather than on clinical efficacy.

When the MMRV/MSD® vaccine was administered to children aged 12 to 23 months serological conversion was induced in 97.4, 95.8, 98.5 and 91.2% for measles, mumps, rubella and varicella, respectively. Seroconversion indices and antibody levels were comparable with those observed in children given the MMR and V vaccines simultaneously in different sites.[36,37]

A subset of the children was given a second dose of the MMRV vaccine around 3 months after the first dose. Geometric mean titers (GMT) of antibodies for measles, mumps and rubella increased by around two times; for varicella, seroconversion reached 99.4%, and GMT increased more than 40 times (from 13.3 to 588.1 gpELISA units/mL).[36,38]

A second dose of the MMRV vaccine was administered at 4 and 6 years of age to children who had previously been given one dose of the MMR and V vaccines when already more than 12 months old. The seroconversion rate observed for varicella after the second dose was 98.9%, with antibody GMT increasing 12 times compared to results from before revaccination.

In the USA the vaccine was licensed to be administered in a single dose to children 12 months to 12 years old and can be given simultaneously with other vaccines recommended for the age group.[36]

The MMRV/GSK® vaccine was studied with children 12 to 18 months old, who were given two doses of the vaccine, with intervals of 6 and 8 weeks (group MMRV) or a dose of MMR simultaneously with a dose of V, followed by another dose of MMR (group MMR + V). After the second dose 100% of the children in both groups exhibited seroconversion for measles, rubella and varicella, while 98% had seroconverted for mumps in the MMRV group and 99% had done so in the MMR + V group.[39]

Another study compared two doses of the MMRV vaccine with two doses of the MMR + V vaccines, given at 9 and 12 months of age. Seroconversion rates were 100% in all children after the second dose (99.2% for mumps in the MMR + V group). Rubella antibody GMT was comparable for the two groups, with GMT for measles, mumps and varicella being higher in the MMRV group.[40]

In Australia, the MMRV/GSK® vaccine was licensed to be used in a two-dose regime, with an interval of 6 to 12 weeks, to be given before the end of the second year of life. The first dose can be given from 9 months of age onwards.

In all these studies, adverse events were similar among children in the MMRV and MMR + V groups. Only mild fever was more common among the children in the MMRV group.[36,40]

Final comments

In Brazil the varicella vaccine has not been added to the routine schedule and is only available free of charge at the CRIE for certain high-risk groups (Table 4). Since the response to varicella vaccine is prejudiced in people with compromised immunoresponse, it is believed that mass vaccination is the best form of protecting at-risk groups since it confers collective immunity.

In 2003, 60 deaths associated with varicella and its complications were registered in the state of São Paulo, with 85% of the victims being children under 5 years old. Studies undertaken in the city of São Paulo revealed that children who attend day care present an increased risk of complications and death when they contract varicella and, for this reason, since 2003, the São Paulo State Health Department mandates vaccination at day care centers (children from 1 to 5 years old) on notification of the first case of varicella.

The varicella vaccine is recommended by the Brazilian Society of Pediatrics and by the Brazilian Society of Immunizations for all non-immune people over 1 year old. From an ethical point of view, health professionals must inform the population of the existence and possible benefits of the varicella vaccine, even when the family has limited economic resources.[6]

We hope that the measles, mumps, rubella, and varicella vaccine will soon be available in Brazil, since the use of combined vaccines facilitates compliance with recommendations for the use of new vaccines and makes wider vaccination coverage possible.

Conflict of interest

Lucia Ferro Bricks declares that she has delivered lectures on vaccines on behalf of the Merck Sharp & Dohme, Sanofi-Pasteur and Wyeth laboratories. She has also participated in research projects and medical congresses sponsored by these laboratories. She is currently one of the investigators working on an international multicenter study into interference between oral rotavirus (MSD pentavalent) and poliomyelitis vaccines, sponsored by the Merck Sharp & Dohme Laboratory. Gabriel Oselka declares that he participates in scientific boards for GSK and Merck Sharp & Dohme Laboratories.

References

1. Centers for Disease Control and Prevention. Prevention of varicella – Update recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 1999;48:1-5.
2. American Academy of Pediatrics. Varicella. In: Pickering LK, editor. Red book 2003 report of the Committee on Infectious Diseases. 26th ed. Elk Groove: American Academy of Pediatrics; 2003.
3. National Advisory Committee on Immunization (NACI) update on varicella. Can Commun Dis Rep. 2004;30:1-26.
4. Marticelli R, Bricks LF. Varicella zoster in children attending day care centers. Clinics. 2006;61:147-52.
5. Clemens SAC, Azevedo T, Fonseca JC, Silva AC, Silveira TR, Clemens R. Soroepidemiologia da varicela no Brasil: resultados de um estudo prospectivo transversal. J Pediatr (Rio J). 1999;75:433-41.
6. Yu ALF, Costa JM, Amaku M, Pannuti CS, Souza VA, Zanetta DM. Three year seroepidemiological study of varicella-zoster virus in São Paulo, Brazil. Rev Inst Med Trop Sao Paulo. 2000;42:125-8.
7. Baldacci ER, Vico ESR. Mortalidade por varicela em crianças atendidas em creche. Pediatria (Sao Paulo). 2002;23:213-6.
8. São Paulo, Secretaria de Estado da Saúde de São Paulo, Centro de Vigilância Epidemiológica Alexandre Vranjac. Vacinação contra varicela em creches. www.cve.saude.sp.gov.br. Access: 21/02/2006.
9. Clements DA, Armstrong CB, Ursano AM, Moggio MM, Walter EB, Wilfert CM. Over five-year follow-up of Oka/Merck varicella vaccine recipients in 465 infants and adolescents. Pediatr Infect Dis J. 1995;14:874-9.
10. Shinefield HR, Black SB, Staehle BO, Matthews H, Adelman T, Ensor K, et al. Vaccination with measles, mumps and rubella vaccine and varicella vaccine: safety, tolerability, immunogenicity, persistence of antibody and duration of protection against varicella in healthy children. Pediatr Infect Dis J. 2002;21:555-61.
11. Kuter B, Matthews H, Shinefield H, Black S, Dennehy P, Watson B, et al. Ten year follow-up of healthy children who received one or two injections of varicella vaccine. Pediatr Infect Dis J. 2004;23:132-7.
12. Krysan DJ. Effectiveness over time of varicella vaccine. J Pediatr.2004;145:416-7.
13. Meurice F, De Bouver JL, Vandevoorde D, Woods S, Bogaerts H. Immunogenicity and safety of a live attenuated varicella vaccine (Oka/SB Bio) in healthy children. J Infect Dis. 1996;174:S324-9.
14. Varis T, Vesikari T. Efficacy of high-titer attenuated varicella vaccine in healthy young children. J Infect Dis. 1996;174:S330-4.
15. Tan AY, Connett CJ, Connett GJ, Quek SC, Yap HK, Meurice F, et al. Use of a reformulated Oka strain varicella vaccine (SmithKline Beecham Biologicals/Oka) in healthy children. Eur J Pediatr. 1996;155:706-11.
16. LaRussa P, Steinberg S, Gershon AA. Varicella vaccine for immunocompromised children: results of collaborative studies in the United States and Canada. J Infect Dis. 1996;174:S320-3.
17. Levin MJ, Gershon AA, Weinberg A, Blanchard S, Nowak B, Palumbo P, et al. Immunization of HIV-infected children with varicella vaccine. J Pediatr. 2001;139:305-10.
18. Sharrar RG, LaRussa P, Galea SA, Steinberg SP, Sweet AR, Keatley RM, et al. The postmarketing safety profile of varicella vaccine. Vaccine. 2000;19:916-23.
19. Lim YJ, Chew FT, Tan AY, Lee BW. Risk factors for breakthrough varicella in healthy children. Arch Dis Child. 1998;79:478-80.

20. Galil K, Fair E, Mountcastle N, Britz P, Seward J. Younger age at vaccination may increase risk of varicella vaccine failure. J Infect Dis. 2002;186:102-5.
21. Verstraeten T, Jumaan AO, Mullooly JP, Seward JF, Izurieta HS, DeStefano F, et al. A retrospective cohort study of the association of varicella vaccine failure with asthma, steroid use, age at vaccination, and measles-mumps-rubella vaccination. Pediatrics. 2003;112:e98-103.
22. Tugwell BD, Lee LE, Gillette H, Lorber EM, Hedberg K, Cieslak PR. Chickenpox outbreak in a highly vaccinated school population. Pediatrics. 2004;113:455-9.
23. Tsolia M, Gershon AA, Steinberg SP, Gelb L. Live attenuated varicella vaccine: evidence that the virus is attenuated and the importance of skin lesions in transmission of varicella zoster virus. National Institute of Allergy and Infectious Diseases Varicella Vaccine Collaborative Study Group. J Pediatr. 1990;116:184-9.
24. Diaz PS, Au D, Smith S, Amylon M, Link M, Smith S, et al. Lack of transmission of the live attenuated varicella vaccine virus to immunocompromised children after immunization of their siblings. Pediatrics. 1991;87:166-70.
25. Seward JF, Zhang JX, Maupin TJ, Mascola L, Jumaan AO. Contagiousness of varicella in vaccinated cases: a household contact study. JAMA. 2004;292:704-8.
26. Centers for Disease Control and Prevention. Outbreak of varicella among vaccinated children – Michigan, 2003. MMWR Morb Mortal Wkly Rep. 2004;53:389-92.
27. Haddad MB, Hill MB, Pavia AT, Green CE, Jumaan AO, De AK, et al. Vaccine effectiveness during a varicella outbreak among schoolchildren: Utah, 2002-2003. Pediatrics. 2005;115:1488-93.
28. Marin M, Nguyen HQ, Keen J, Jumaan AO, Mellen PM, Hayes EB, et al. Importance of catch-up vaccination: experience from a varicella outbreak, Maine, 2002-2003. Pediatrics. 2005;115: 900-5.
29. Davis MM, Patel MS, Gebremariam A. Decline in varicella-related hospitalizations and expenditures for children and adults after introduction of varicella vaccine in the United States. Pediatrics. 2004;114:786-92.
30. Zhou F, Harpaz R, Jumaan AO, Winston CA, Shefer A. Impact of varicella vaccination on health care utilization. JAMA. 2005;294:797-802.
31. Nguyen HQ, Jumaan AO, Seward JF. Decline in mortality due to varicella after implementation of varicella vaccination in the United States. N Engl J Med. 2005;352:450-8.
32. Mor M, Harel L, Kahan E, Amir J. Efficacy of postexposure immunization with live attenuated varicella vaccine in the household setting – a pilot study. Vaccine. 2004;23:325-8.
33. Jumaan AO, Yu O, Jackson LA, Bohlke K, Galil K, Seward JF. Incidence of herpes zoster, before and after varicella-vaccination-associated decreases in the incidence of varicella, 1992-2002. J Infect Dis. 2005;191:2002-7.
34. Yih WK, Brooks DR, Lett SM, Jumaan AO, Zhang Z, Clements KM, et al. The incidence of varicella and herpes zoster in Massachusetts as measured by the Behavioral Risk Factor Surveillance System (BRFSS) during a period of increasing varicella vaccine coverage, 1998-2003. BMC Public Health. 2005;5:68.
35. Oxman MN, Levin MJ, Johnson GR, Schmader KE, Straus SE, Gelb LD, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med. 2005;352:2271-84.
36. Centers for Disease Control and Prevention. Licensure of a combined live attenuated measles, mumps, rubella, and varicella vaccine. MMWR. 2005;54:1212-4.
37. Shinefield H, Black S, Digilio L, Reisinger K, Blatter M, Gress JO, et al. Evaluation of a quadrivalent measles, mumps, rubella and varicella vaccine in healthy children. Pediatr Infect Dis J. 2005;24:665-9.
38. Shinefield H, Black S, Williams WR, Marchant C, Reisinger K, Stewart T, et al. Dose-response study of a quadrivalent measles, mumps, rubella and varicella vaccine in healthy children. Pediatr Infect Dis J. 2005;24:670-5.
39. Knuf M, Habermehl P, Zepp F, Mannhardt W, Kuttnig M, Muttonen P, et al. Immunogenicity and safety of two doses of tetravalent measles-mumps-rubella-varicella vaccine in healthy children. Pediatr Infect Dis J. 2006;25:12-8.
40. Goh P, Han H, Willems P, Descamps D, Emmanuel S, Meurice F. Safety and immunogenicity of a two-dose measles-rubella-varicella (MMRV) vaccine at 9 and 12 months of age. In: European Society of Pediatric Infections Diseases Congress; 2005 May; Valencia, Spain.

Correspondence:
Lucia Ferro Bricks
Instituto da Criança – HCFMUSP
Av. Dr. Enéas de Carvalho Aguiar, 647
CEP 05403-900 - São Paulo, SP – Brazil
Tel./Fax: +55 (11) 3069.8503
E-mail: lfbricks@gmail.com