La varicelle : actualités
Chickenpox: an update

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Résumé

Malgré son caractère bénin, la varicelle est une pathologie de l'enfance responsable de complications et de décès, notamment au sein des populations à haut risque. Le VariZIG®, non commercialisé en France, est une bonne alternative chez les personnes séronégatives exposées au virus et non éligibles à la vaccination. L'efficacité de la vaccination en systématique a été démontrée par une diminution de l'incidence de la varicelle et le développement d'une immunité de groupe. Au fil des années, le taux d'anticorps protecteurs chez les personnes vaccinées diminue et peut être maintenu par la vaccination à deux doses. Un vaccin tétravalent rougeole-oreillons-rubéole-varicelle, utilisé aux États-Unis, présente une bonne tolérance malgré la survenue de fièvres et de convulsions fébriles. La vaccination en routine permettrait à la France de réaliser une économie, en diminuant les coûts directs et indirects entraînés par la varicelle, qui demeure aujourd'hui un problème de santé publique.

Abstract

Despite its benign characteristics, chickenpox is a childhood disease responsible for complications and deaths, particularly in the high-risk population. VariZIG®, not commercialized in France, is a good alternative for seronegative individuals exposed to the virus and not eligible for vaccination. The efficacy of routine vaccination has been demonstrated with a decrease in chickenpox incidence and with the development of herd immunity. Over time, the protective antibody titer of vaccinated people decreases and can be maintained by two doses of the vaccine. A tetravalent measles-mumps-rubella-chickenpox vaccine, used in the United States, has a good tolerability in spite of the occurrence of fever and febrile seizures. Routine vaccination would contribute to make savings in France, by reducing direct and indirect costs of chickenpox.

Chickenpox is a highly contagious airborne disease caused by the varicella zoster virus (VZV) [1-3]. Most often benign and self-limiting, chickenpox is one of the most common childhood diseases and is characterized by a blister-like rash and fever [4]. Chickenpox may be complicated by a secondary bacterial infection, pneumonia, or encephalitis especially in adolescents, adults, and immunocompromised subjects [5,6]. The mortality rate of the 15-44 year age group is 20 times higher than that of the 5-14 year age group in England and Wales. A total of 0.94 deaths per 100,000 inhabitants is indeed observed in people aged 5-14 years versus 20.06 in those aged 15-44 years [7]. Subjects aged above 13 years have a 2.2-fold increased risk of contracting moderate to severe chickenpox compared with infants [8]. Pregnant women infected with VZV may face complications and severe consequences for the fetus [9]. A total of 676,971 cases of chickenpox were reported in France in 2012. Most of them occurred in children aged 1-4 years, 1.8% presented with complications, and 0.2% had to be hospitalized [10].

A vaccine is available and may prevent disease onset. Various countries such as the United States, Canada, and Japan have included the routine vaccination of infants against chickenpox in their vaccination schedule [3]. In Canada, the two-dose universal vaccination of infants aged 12-15 months has been recommended by the National Advisory Committee on Immunization since 2010 [9].

Routine vaccination of children is not recommended in France. Two live attenuated monovalent vaccines are available: Varilrix® and Varivax®. Two doses are recommended in adolescents aged 12-18 years and in high-risk populations without any clinical history of chickenpox such as women of childbearing potential, immunocompetent adults within three days of VZV exposure, people with close contact with immunocompromised subjects, and

children who underwent solid organ transplantation. Vaccination is also recommended to all healthcare professionals with no history of chickenpox [6,11].

1. Chickenpox complications

Chickenpox in infants may lead to complications when it occurs in-between the loss of the maternal antibodies and the recommended age for vaccination.

An inverse correlation has been observed between the level of circulating maternal anti-VZV antibodies in infants aged below one year contracting chickenpox and the onset of complications [12]. Cutaneous complications are most common and account for 65% of complications in infants aged below one year and for 60% in children aged 1-4 years. Neurological complications prevail (55%) in children aged 5-14 years, while pulmonary complications are observed in 68% of children aged over 14 years [10]. Chickenpox complications are common in high-risk populations such as immunocompromised individuals. Twenty per cent of autologous hematopoietic stem cell graft recipients contract chickenpox. Chickenpox is usually characterized by a rash and may lead to severe complications such as postherpetic neuralgia or secondary bacterial infection [13]. VZV infection in pregnant women between the 8th and the 20th weeks of gestation may lead to congenital varicella syndrome which is characterized by low birth weight and fetus malformations [14]. The case fatality among newborns presenting with congenital varicella syndrome is 30% during the first few months of life, and the risk of herpes zoster infection is estimated at 15% during the first four years of life. Newborns contract a severe infection when the mother contracts chickenpox between five days before and two days after giving

birth. A less severe infection is observed when the mother has been exposed to the VZV virus at least five days before giving birth [15,16].

Complications caused by the VZV virus require patients to be hospitalized. Overall, 32.6% of hospitalizations relate to patients presenting with chickenpox complicated by a skin and soft tissue bacterial infection (pyoderma, cellulitis, abscess), 29.9% to patients with neurological complications (cerebellar ataxia, seizures), and 21.7% to patients with pneumonia complications [12].

Healthcare professionals may be in contact with high-risk individuals and can therefore transmit the disease. A seroprevalence study conducted with healthcare professionals in Iran revealed that 6.7% of them were not immunized against chickenpox. Of 291 individuals remembering having had chickenpox in their childhood, only 278 had a positive serology for VZV (95.5%). Remembering having had chickenpox during childhood is not indicative of immunity. This study highlights the need to routinely investigate VZV serology in healthcare professionals, and to recommend vaccination to seronegative individuals - as it is associated with higher costs - to avoid virus transmission to hospitalized patients [17].

2. Prophylaxis

Following exposure to VZV, the transmission rate of chickenpox is 90%. Early management of patients presenting with chickenpox is therefore crucial to avoid secondary cases in high-risk populations. Effective treatment with acyclovir (10 mg/kg IV every 8 hours) and cefotaxime (1 g IV every 12 hours) for 7 days, combined with hygiene precautions such as disinfecting soiled material, has proved effective in reducing virus transmission and in preventing the emergence of post-exposure cases (Table I). No secondary cases of chickenpox was thus observed in Caspian's study following the implementation of prevention and control

measures after detection of the primary case patient [18]. Hematopoietic stem cell transplant recipients are at higher risk of contracting chickenpox because of their immunosuppression. A recent study highlighted the low incidence of chickenpox in a cohort of 141 patients following long-term administration of acyclovir 200 mg until completion of the immunosuppressant treatment and for at least one year following transplant. Only 2.3% of transplant recipients who complied with treatment contracted chickenpox during the year following transplant, and 14.8% during the two years following transplant. When transplant recipients did not comply with treatment, 27.3% contracted chickenpox during the year following transplant and 54.5% during the two years following transplant [13]. Oral treatment with acyclovir 1,000 mg/day for 35 days following hematopoietic stem cell transplantation, followed by low doses of oral valaciclovir (500 mg three times a week) up to one year after transplant, significantly reduced the risk of contracting chickenpox (5.7% of chickenpox cases among patients who complied with the prophylaxis) [19].

The US Food and Drug Administration (FDA) approved the use of VariZIG® in 2012. VariZIG® is a preparation of purified immunoglobulins targeted against VZV and prepared from human plasma. VariZIG® is for VZV post-exposure use in seronegative individuals at high risk of complications as compared with the general population. VariZIG® contains 5% of IgG and can be administered through the intramuscular route at a dose of 125 IU/10 kg, with a maximum dose of 625 IU. The minimum dose is 62.5 IU for patients weighing <2 kg and 125 IU for patients weighing 2-10 kg [3]. Patients must be informed of the potential risks and benefits of the prophylaxis. They must also give consent before receiving the product [20]. Administration of VariZIG® within 10 days of exposure reduces the risk of contracting clinical chickenpox or asymptomatic infection. Twenty per cent of children exposed to VZV after VariZIG® administration presented with clinical chickenpox versus 90% of those who did not

receive VariZIG, and 5% presented with an asymptomatic infection. A study revealed the correlation between the time interval from exposure to administration of VariZIG® and the incidence of the disease. VariZIG® administration within 96 hours following VZV exposure was associated with optimal efficacy. Clinical symptoms were always attenuated following VariZIG® administration, irrespective of the time of administration [20,21]. VariZIG® can be administered to exposed VZV-seronegative pregnant women, and it may contribute to reducing the incidence and severity of congenital varicella syndrome. Several studies reported no congenital varicella syndrome in pregnant women who contracted chickenpox after having received VariZIG® versus 2.81% in those who did not receive VariZIG® [22,23].

In Europe anti-VZV human immunoglobulins are commercialized under the name of Varitect®. They must also be administered within 96 hours of exposure, but through intravenous infusions at a dose of 0.1 to 1 ml/kg/hour (i.e., 5-25 IU/kg/hour). In France Varitect® is prescribed as part of a temporary marketing authorization (French acronym ATU) on a case-by-case basis [24-26].

3. Routine vaccination

3.1 Impact on the incidence of chickenpox

Chickenpox vaccination was authorized in the United States in 1995. The national Advisory Committee on Immunization Practices initially recommended the routine administration of a single dose of vaccine to infants aged 12-18 months, to children aged 19 months to 12 years susceptible to VZV, and to high-risk populations. A 9 to 10-fold decreased risk of contracting chickenpox has been demonstrated in vaccinated children as compared with unvaccinated children. A total of 3,921 cases were reported in Philadelphia between January 1995 and

December 2005. The number of chickenpox cases dropped from 4.1 cases per 1,000 inhabitants in 1995 to 0.4 cases per 1,000 inhabitants in 2005. The all-age incidence therefore dropped by 90.4% [1,28]. Routine vaccination was also implemented in China and led to a decreased incidence of chickenpox (from 7.14 cases to 0.76 cases per 1,000 person-years between 2000 and 2009) [29].

A study performed in Saudi Arabia revealed the impact of the chickenpox vaccine introduction in 1998 as well as that of mandatory vaccination in 2008.

Before vaccine introduction, i.e. between 1994 and 1997, 10,070 cases of chickenpox were reported. Vaccine introduction contributed to reducing the number of chickenpox cases by approximately 10% from 1998 to 2007. Introducing the chickenpox vaccine in the vaccination schedule in 2008 contributed to significantly decreasing the number of chickenpox cases (i.e. 1,577 cases reported between 2008 and 2011). Overall, the mandatory vaccination decreased the incidence of the disease from 355 in 1998 to 88.1 cases in 2011 (per 100,000 inhabitants). The mandatory vaccination program against chickenpox thus contributed to decreasing the incidence of the disease by 84% [30].

This decreased incidence obtained with the introduction of a routine administration of a single dose vaccine was also observed in Sicily; the incidence of chickenpox indeed dropped by 95.7% since 2003 [4]. Introducing routine vaccination in various countries led to a significant decrease in the incidence of chickenpox and modified the mean age of chickenpox onset. In Saudi Arabia 8.3% of cases of chickenpox reported between 1994 and 1997 in unvaccinated children, were observed in infants aged below one year. Between 1998 and 2007, following introduction of the chickenpox vaccine, that same population only accounted for 5.4% of chickenpox cases. Between 2008 and 2011, when chickenpox vaccination became mandatory, 3.8% of infants aged below one year contracted the disease.

The incidence of chickenpox among infants aged below one year thus decreased by 54% between 1994 and 2011. The incidence of the disease dropped from 41.3% to 16.8% among children aged 1-4 years between the pre-vaccination period and the implementation of mandatory vaccination; a 60% reduction of chickenpox incidence was therefore observed in that age group [29]. The same trend was observed in the United States with a higher decrease (by 95%) in chickenpox incidence among children aged 1-9 years [27]. On the contrary, the number of chickenpox cases increased in adults aged over 40 years; they accounted for 2.2% of chickenpox cases between 1994 and 1997 versus 11.5% between 2008 and 2011 [30].

This decreased incidence of the disease is due to the increased vaccination coverage obtained with routine vaccination of infants and with catch-up vaccination for susceptible adolescents. The vaccination coverage reported in Philadelphia between 1997 and 2005 increased from 41% to 94% among infants aged 19-35 months. An Australian study indicated that vaccinating infants increased the vaccination coverage from 20% to 83% in this population. High vaccination coverage is associated with herd immunity, which contributes to decreasing the incidence of the disease in infants who are not eligible for vaccination as well as in adults [28,31].

3.2 Rates of outpatient visits and hospitalizations

Very few severe chickenpox cases have been reported in the 14 years following the implementation of chickenpox vaccination in the United States [1]. In Germany an 84% decrease in the number of complicated cases of chickenpox was observed, mainly among children aged below 9 years [32]. The rate of secondary complications due to chickenpox

decreased by 47% following recommendations for routine vaccination. The number of outpatient visits for chickenpox decreased by 65.8% following the implementation of routine vaccination. This decreased number of outpatient visits is due to the decreased incidence of the disease among children aged below 14 years. The number of outpatient visits for chickenpox among children aged below 4 years dropped from 576.1 to 11.4 per 100,000 inhabitants between 1995 and 2001 and from 269.3 to 30.7 per 100,000 inhabitants among children aged 5-14 years. During this period the total number of hospitalizations for chickenpox decreased by 53.1%. Following vaccine introduction, 14.5 hospitalizations per 100,000 inhabitants were chickenpox-related versus 30.9 before. The number of hospitalizations decreased from 29.7 per 100,000 inhabitants in 1995 to 10.5 in 2001, and six in 2004. The highest decrease in the rate of hospitalizations was observed among children aged below 14 years [33]. A 72% drop in the rate of hospitalizations was observed among children aged below 4 years. Mean age of hospitalized patients following chickenpox increased from 14 to 22 years. The number of chickenpox-related hospitalizations of patients presenting with at least one comorbidity decreased from 19.2% to 15.3% [34]. Overall, 54.6% of hospitalized patients present with at least one complication versus 65.4% before vaccine introduction [15]. Routine vaccination had an impact on the mean hospital length of stay, which depends on the patient's state: the mean length of stay observed since vaccination introduction is 4.6 days versus 5.4 days before vaccine introduction (this data does not take into account the vaccination status of hospitalized patients). This difference in the mean length of stay is due to the decreased rate of complications and to the decreased duration of the infection [34]. In Spain routine vaccination of infants aged 15-18 months contributed to decreasing the rate of hospitalizations by 78%, mainly among children aged below 5 years with 46.77 hospitalizations per 100,000 inhabitants in 2006 and 26.55 in 2010

[35]. An Australian study reported similar results with an 80% decrease in chickenpox-related hospitalizations irrespective of age, following introduction of the vaccine in the vaccination schedule in 2006 [3]. This decrease was most significant among children aged 1-4 years who represent the age cohorts that were offered vaccination, with a risk ratio of 0.17. This risk ratio is 0.26 for infants aged below 1 year, 0.34 for children aged 5-9 years, and 0.36 for adolescents aged 10-19 years. A decreased rate of hospitalizations was also observed among adults aged 20-59 years and was indicative of a decreased virus circulation induced by herd immunity [36].

A significant decrease in the rate of outpatient visits and hospitalizations has thus been observed since the introduction of routine chickenpox vaccination in several countries [4].

4. Routine administration of two doses of vaccine

4.1. One dose is not enough

It has been showed that the rate of protective antibodies decreases over the years following the one-dose vaccination [37].

Children may thus contract chickenpox despite having received the one-dose vaccine, with a peak of infection between 6 and 9 years. The number of chickenpox cases increases with years following vaccination among children vaccinated between 12 months and 12 years. Thus, a total of 1.6 cases of chickenpox per 1,000 person-years is reported in the year following vaccination. A total of nine cases per 1,000 person-years is reported in the five years following vaccination, 20.4 cases in the eight years following vaccination, and 58.2 cases in the nine years following vaccination [8].

A study was performed in a school setting where 99% of children had been vaccinated with a single dose of the chickenpox vaccine. A two-month chickenpox epidemic highlighted that coverage with a single dose of vaccine was not enough to avoid virus transmission [38].

The introduction of the chickenpox vaccine in the vaccination schedule is hampered by the risk of a shift of contamination to higher age groups. Mean age of chickenpox onset among children, irrespective of the vaccination status, indeed increased following introduction of the routine single dose vaccine. Mean age of chickenpox onset among vaccinated children increased from 5 to 8 years and from 5 to 13 years among unvaccinated children. This higher age of onset has clinical consequences as chickenpox in adolescents or adults is associated with more severe complications than in young children [28]. Children whose vaccination is older than five years have a 1.4-fold increased risk of contracting moderate to severe chickenpox than children who received the vaccine in the past 5 years. Chickenpox severity increases as time following administration of the single dose vaccine goes by, and the rate of antibodies induced by the single dose vaccine seems to decrease 5 years after vaccination [8,39].

4.2. Two doses of the chickenpox vaccine are required

The second dose of the vaccine was introduced in the vaccination schedule of the United States in 2006 by the Centers for Disease Control and Prevention (CDC). A routine two-dose vaccination strategy against chickenpox is associated with a decreased incidence of the disease and with a decreased rate of hospitalizations. The risk of contracting chickenpox is estimated at 95% two years and a half after receiving the two-dose vaccine. This figure is lower than that observed two years and a half after receiving the single dose vaccine [40]. In

2010 the incidence of the disease and related hospitalizations decreased by 98% and 85% respectively, compared with 1995 [41]. The incidence of chickenpox decreased by 43.3% when the single dose vaccination was implemented between 2006 and 2010, and then by 71.6% when the routine two-dose vaccination was recommended [42]. Introducing a second dose in the vaccination schedule contributed to decreasing the incidence of chickenpox by 59.3% among children aged 1-4 years and by 82.3% among children aged 5-9 years [14]. The routine administration of the two-dose vaccine improves immunity. The efficacy of two doses of vaccine administered 42 days apart is estimated at 99.5% for moderate to severe cases of chickenpox and at 94.9% for all presentations. A 3.3-fold decreased risk of contracting chickenpox is observed 42 days after vaccination with two doses as compared with the single dose vaccine. The rate of anti-VZV antibodies is 18 times higher 42 days after administration of the second dose than 42 days after the single dose administration. Overall, 99% of children receiving two doses of vaccine have the required antibodies for protection against chickenpox six weeks after vaccination versus 86% of children vaccinated with the single dose vaccine [2,38]. A high number of VZV seropositive individuals are responsible for herd immunity which is beneficial to children who are not eligible for vaccination and to immunocompromised adults. The routine administration of two doses thus contributed to decreasing the incidence of epidemics by 95%, from 236 epidemics in 1995 to 12 epidemics in 2010 [41]. The efficacy of the two-dose vaccine is sustained over time. Overall, 96.1% of subjects receiving both doses have a protective rate of anti-VZV antibodies two years after vaccination versus 78.2% of subjects only receiving one dose. The risk of contracting chickenpox two years after having received both doses of the vaccine is therefore lower than that observed with the single dose vaccine. Two doses of the chickenpox vaccine provide effective protection and decrease the rates of morbidity and mortality [2,38].

5. A combined vaccine for measles-mumps-rubella-chickenpox (MMRC)

Routine vaccination against chickenpox (C) with a monovalent vaccine would potentially be implemented in the same age group as that for vaccination against measles, mumps, and rubella (MMR). In France the authorization of the tetravalent MMRC vaccine (measles-mumps-rubella-chickenpox) would contribute to improving vaccination coverage by facilitating the introduction of the chickenpox vaccine in the pediatric vaccination schedule and by decreasing the required number of injections [43,44].

Recommendations were updated in 2011 in Germany. The combined MMRC vaccine has been recommended in routine practice since 2004. However, considering the risk of febrile seizures, health authorities recommended the separate vaccination of MMR and chickenpox in 2011. A study revealed that these new recommendations led to a decreased number of chickenpox vaccination, from 4% to 12% for the first dose and from 15% to 19% for the second one. This decrease was highest among children aged 2-9 years with a 30% decrease in vaccinations. On the contrary, no decrease in MMR vaccinations was observed [45,46].

5.1. Tolerability

In 2005, the use of the combined MMRC vaccine was authorized by the FDA in the United States. The main risk of this combined vaccine is febrile seizures. Between February 2006 and August 2007, 84.6 cases of febrile seizures per 1,000 children-years were reported among children vaccinated with the MMRC vaccine versus 42.2 cases of febrile seizures per 1,000 children-years among children vaccinated with the MMR vaccine and with the

chickenpox monovalent vaccine (MMR+C). The risk of febrile seizures is twice higher with the MMRC vaccine than with the MMR+C vaccines [43].

A Korean study confirmed this data by comparing the rate of fever episodes among children aged 11-24 months vaccinated with the MMR vaccine and the C vaccine or with the MMRC vaccine. The number of fever episodes was significantly higher in children receiving the combined MMRC vaccine during the first 15 days following vaccination: 28.3% of fever episodes in the MMRC group and 25.9% of fever episodes in the MMR+C group with the administration of the first dose, and 20.2% in the MMRC group and 24.2% in the MMR+C group with the administration of the second dose. A prevalence peak was observed between Day 5 and Day 12 following vaccination. The number of fever episodes observed during the 43 days of follow-up of vaccinated children remained higher in the MMRC group and after administration of the first dose [44,47]. The incidence of Grade 3 fever episodes remained low during the 15 days following vaccination: 12.3% in the MMRC group versus 6.9% in the MMR+C group. When the second dose of the MMRC vaccine was administered, 24.8% of patients presented with red patches at the injection site, 31% with fever including 12.9% of Grade 3 fever [46]. The incidence of fever differs by age (Table II). It is higher in children aged 15-24 months than in those aged 2-6 years, following the administration of each dose. Red patches at the injection site was the most frequent symptom reported after the administration of each dose: 28.2% in the MMRC group and 15.7% in the MMR+C group. The incidence of this local reaction, irrespective of the grade, was significantly higher in the group receiving the first dose of the MMRC vaccine. Grade 3 red patches (diameter >20 mm) were observed in 1.8% of patients vaccinated with the first dose of the MMRC vaccine and in 1.3% of patients vaccinated with the first dose of the MMR+C vaccines.

No significant difference was observed in terms of Grade 3 red patches between both groups [44].

The rate of patients who received antibiotics and antipyretic drugs was 37.5% in the MMRC group versus 35% in the MMR+C group following administration of the first dose, and 37.6% and 32.8% respectively following administration of the second dose [46].

5.2. Immunogenicity

A study compared the administration of a first dose of the MMRC vaccine and of the MMR+C vaccines followed by a second dose of the monovalent chickenpox vaccine in two groups of seronegative children. Following vaccination, the rate of anti-VZV antibodies increased by a factor of 14.1 and 12.6 in children aged 15-24 months and 2-6 years in the MMRC group, and of 9.8 and 13.1 in the MMR+C group [44]. The intensity of the immune response six weeks after vaccination with a single dose of MMRC vaccine is as high as that provided by a single dose of the chickenpox monovalent vaccine associated with the MMR vaccine in children aged 4-6 years [48]. Both types of vaccine provide an equivalent titer of anti-VZV antibodies [2,44]. Two years after vaccination, the number of seropositive children for VZV was higher in the MMRC group than in the MMR+C group. A total of 97.3% of children vaccinated with the combined MMRC vaccine had anti-VZV antibodies versus 90.7% of those vaccinated with the MMR+C vaccines [46].

6. Impact of vaccination on the incidence of herpes zoster infection

Infection with VZV confers a specific T-cell-mediated immunity. This immunity decreases in elderly people and in immunocompromised individuals and may trigger virus reactivation as

it latently persists in sensitive lymph nodes for several decades [49]. This reactivation is responsible for a localized blister-like skin rash associated with acute pain, i.e. herpes zoster infection [10,50,51]. Chickenpox vaccination accentuates this immune response, reduces the number of chickenpox cases and the risk of virus reexposure. Chickenpox vaccination could therefore be correlated with an increased incidence of herpes zoster infections [49,52]. A Chinese study reported an increased incidence of herpes zoster infections from 4 to 6 cases per 1,000 person-years between the years 2000 and 2009 [28]. The incidence of herpes zoster infections is nevertheless believed to be linked to various factors such as the age at vaccination and the duration of immunity. The risk of contracting a herpes zoster infection increases in children vaccinated after 5 years of age [53]. A study conducted in the United States between 1993 and 2006 revealed that the incidence of herpes zoster infection did not significantly differ between adults living in states with low vaccination coverage and those living in states with high vaccination coverage [54]. An algorithm able to predict the impact of two doses of the chickenpox vaccine on the incidence of herpes zoster infections highlighted an increased incidence by almost 30% the first 20 years following vaccination. This incidence should then reduce with the aging of the vaccinated population and with the reduced proportion of people with a history of chickenpox. Routine chickenpox vaccination should help eradicate herpes zoster in the long run [55,56]. A herpes zoster vaccine was authorized in the United States in 2006; it should contribute to reducing the incidence and severity of the disease [57].

7. Costs avoided by vaccination

Arguments related to chickenpox hospitalization costs favor the introduction of the chickenpox vaccine in the vaccination schedule. Besides the benefits for the patient's health, the routine vaccination contributes to reducing healthcare-associated costs [12,58]. Routine chickenpox vaccination prevented 73 premature deaths and 3,942,546 cases of chickenpox between 2000 and 2010 in the United States [58]. A Japanese study reported that chickenpox was the third infection associated with the highest number of hospitalizations, with a mean cost of 1,967 Euros per person. The benefit-cost ratio is four times higher with routine vaccination [59]. The annual direct cost associated with chickenpox hospitalizations in Turkey is estimated at 288,235 Euros and 70% of these hospitalizations involve children without any contraindications to vaccination. More than half of them (64.2%) are aged below one year. Neurological complications are associated with the highest costs. Chickenpox vaccination helped save 1,598 million of dollars in global societal costs in the United States between 2000 and 2010 [12,60].

The proportion of indirect costs such as absenteeism and loss of productivity (missed days of work for the parents) accounts for an important part of the global costs. The number of missed days of work estimated by parents to take care of their sick children ranges from 0.6 to 5 days [39].

A study detailed the costs of various vaccination programs. Direct costs associated with the vaccination of adolescents and adults not immunized against chickenpox were 1.43 million Euros, and indirect costs were 4.7 million Euros. The routine chickenpox vaccination of infants contributes to reducing the costs - both direct and indirect - by 58%. The two-dose vaccination is associated with an even greater reduction: 64% [61].

8. Conclusion

The general population believes chickenpox to be a benign disease. It is, however, responsible for a substantial proportion of hospitalizations and deaths. Adequate prophylaxis and vaccination coverage of at least 90% contribute to avoiding complications in the high-risk population. Such vaccination coverage may be obtained by implementing routine vaccination with the MMRC tetravalent vaccine and by achieving sustained immunity with the administration of two doses of the vaccine. This vaccine should soon be available in France and should contribute to increasing the number of vaccinations.

Conflicts of interest

The authors report no conflict of interest.

Contribution of authors

LO PRESTI C wrote the article.

CURTI C, MONTANA M, BORNET C, and VANELLE P reviewed the article.

References

1. Baxter R, Ray P, Tran TN, Black S, HR, Coplan PM, et al. Long-term effectiveness of varicella vaccine: a 14-Year, prospective cohort study. *Pediatrics*. 2013 May ;131(5):e1389-96.
2. Prymula R, Bergsaker MR, Esposito S, Gothefors L, Man S, Snegova N, et al. Protection against varicella with two doses of combined measles-mumps-rubella-varicella vaccine versus one dose of monovalent varicella vaccine: a multicentre, observer-blind, randomised, controlled trial. *Lancet*. 2014 Jan 28. pii: S0140-6736(12)61461-5.
3. Park CS, Kim DS, Kim KH. Varicella outbreak in the patients during group therapy: seroprevalence in a healthcare system during breakthrough varicella occurrence. *Clin Exp Vaccine Res* 2013 Jul;2(2):140-3.
4. G Giammanco, S Ciriminna, I Barberi, L Titone, M Lo Giudice, L R Biasio. Universal varicella vaccination in the Sicilian paediatric population: rapid uptake of the vaccination programme and morbidity trends over five years. *Eurosurveillance*, Volume 14, Issue 35, 03 September 2009
5. Heininger U, Seward JF. Varicella. *Lancet* 2006 Oct 14;368(9544):1365-76.
6. Floret D. Immunization against Varicella. *Therapie* 2005 May-Jun;60(3):275-82.
7. Rawson H, Crampin A, Noah N. Deaths from chickenpox in England and Wales 1995-7: analysis of routine mortality data. *BMJ*. 2001 Nov 10;323(7321):1091-3.
8. Chaves SS, Gargiullo P, Zhang JX, Civen R, Guris D, Mascola L, Seward JF. Loss of vaccine-induced immunity to varicella over time. *N Engl J Med* 2007 Mar 15.
9. Field N, Amirthalingam G, Waight P, Andrews N, Ladhani SN, van Hoek AJ et al. Validity of a reported history of chickenpox in targeting varicella vaccination at susceptible adolescents in England. *Vaccine*. 2014 Feb 26;32(10):1213-7.
10. Sentinelles. Bilan annuel 2012. <http://websenti.u707.jussieu.fr/sentiweb/?page=bilan>. Accessed on February 22, 2014 (100 pages).
11. Calendrier vaccinal et recommandations vaccinales 2013 du ministère des Affaires sociales et de la Santé, selon l'avis du Haut conseil de la santé publique. http://www.sante.gouv.fr/IMG/pdf/Calendrier_vaccinal_detaille_2013_ministere_Affaires_sociales_et_Sante_.pdf. Accessed on February 23, 2014 (52pages).
12. Campbell S, Crawford NW. Varicella infection in infants less than 12 months. *Vaccine* 31; 2013. 295-296.

13. Turel O, Bakir M, Gonen I, Hatipoglu N, Aydogmus C. Children Hospitalized for Varicella: Complications and Cost Burden. *Value in health regional issues* 2. 2013; 226-230.
14. Kawamura K, Wada H, Yamasaki R, Ishihara Y, Sakamoto K, Ashizawa M et al. Prophylactic role of long-term ultra-low-dose acyclovir for varicella zoster virus disease after allogeneic hematopoietic stem cell transplantation. *Int J Infect Dis* 2014 Feb;19:26-32.
15. Sengupta N, Booy R, Schmitt HJ, Peltola H, Van-Damme P, Schumacher RF, Campins M, Rodrigo C, Heikkinen T, Seward J, Jumaan A, Finn A, Olcén P, Thiry N, Weil-Olivier C, Breuer J. Varicella vaccination in Europe: are we ready for a universal childhood programme? *Eur J Pediatr* 2008 Jan;167(1):47-55.
16. Sharma CM, Sharma D. A classical case of neonatal varicella. *J Clin Neonatol*. 2013 Oct;2(4):200.
17. Soman R, Madan S. Chickenpox: docile or deadly? *J. Postgrad Med* 2013 apr-jun;59(2): 91-2.
18. Caspian J. Seroepidemiology of varicella zoster virus in healthcare workers in Babol, Northern Iran. 2013; 4(3): 686-691.
19. Shrivastava SR, Shrivastava PS, Ramasamy J. Epidemiological investigation of a case of chickenpox in a medical college in Kancheepuram, India. *Germes*. 2013 March; 3(1): 18-20.
20. Centers for Disease Control and Prevention (CDC). A new product (VariZIG) for postexposure prophylaxis of varicella available under an investigational new drug application expanded access protocol. *MMWR Morb Mortal Wkly Rep* 2006 Mar 3;55(8):209-10.
21. CDC: Updated recommendations for use of VariZIG -- United States, 2013. *MMWR* 2013;62:574-6.
22. Ghosh S, Chaudhuri S. Pregnancy and varicella infection: a resident's quest. *Indian J Dermatol Venereol Leprol*. 2013 Mar-Apr
23. Cohen A, Moschopoulos P, Stiehm RE, Koren G. Congenital varicella syndrome: the evidence for secondary prevention with varicella-zoster immune globulin. *CMAJ*. 2011 Feb 8;183(2):204-8.
24. Macé G, Gallot V, Vauloup-Fellous C, Picone O. [Chickenpox during pregnancy: development]. *J Gynecol Obstet Biol Reprod (Paris)*. 2008 Mar;37 Suppl 1:22-8.
25. ANSM. Agence Nationale de Sécurité du Médicament et des produits de santé. Spécialités pour lesquelles des ATU nominatives ont été octroyées en 2013. Publié le 17 février 2014. Accessed on May 26, 2014. <http://ansm.sante.fr/Activites/Autorisations-Temporaires-d-Utilisation-ATU/L-ATU-nominative/%28offset%29/2>.

26. OMEDIT de Haute-Normandie. L'Observatoire du Médicament, des Dispositifs médicaux et des Innovations Thérapeutiques. Guide des antidotes et médicaments d'urgence. Publié le 6 mai 2013. Accessed on May 26, 2014. http://www.omedit-hautenormandie.fr/Files/guide_des_antidotes_et_des_medicaments_d_urgence_v.avril_2013.pdf
27. Charlier C, Le Mercier D, Salomon LJ, Ville Y, Kermorvant-Duchemin E, Frange P. Varicella-zoster virus and pregnancy. *Presse Med.* 2014 Jun;43(6 Pt 1):665-75. doi: 10.1016/j.lpm.2014.04.001. Epub 2014 May 23.
28. Guris D, Jumaan AO, Mascola L, Watson BM, Zhang JX, Chaves SS, Gargiullo P, Perella D, Civen R, Seward JF. Changing varicella epidemiology in active surveillance sites--United States, 1995-2005. *J Infect Dis* 2008 Mar 1;197
29. Wu PY, Wu HD, Chou TC, Sung FC. Varicella vaccination alters the chronological trends of herpes zoster and varicella. *PLoS One.* 2013 Oct 30;8(10):e77709
30. Al-Tawfiq JA, AbuKhamis A, Memish ZA. Epidemiology and impact of varicella vaccination: a longitudinal study 1994-2011. *Travel Med Infect Dis* 2013 Sep-Oct;11(5):310-4
31. Ward K, Dey A, Hull B, Quinn HE, Macartney K, Menzies R. Evaluation of Australia's varicella vaccination program for children and adolescents. *Vaccine.* 2013 Feb 27;31(10):1413-9.
32. Spackova M, Muehlen M, Siedler A. Complications of varicella after implementation of routine childhood varicella vaccination in Germany. *Pediatr Infect Dis J* 2010 Sep;29(9):884-6
33. Shah SS, Wood SM, Luan X, Ratner AJ. Decline in varicella-related ambulatory visits and hospitalizations in the United States since routine immunization against varicella. *Pediatr Infect Dis J* 2010 Mar;29(3):199-204
34. Lopez AS, Zhang J, Brown C, Bialek S. Varicella-related hospitalizations in the United States, 2000-2006: the 1-dose varicella vaccination era. *Pediatrics.* 2011 Feb;127(2):238-45.
35. Gil-Prieto R, Walter S, Gonzalez-Escalada A, Garcia-Garcia L, Marín-García P, Gil-de-Miguel A. Different vaccination strategies in Spain and its impact on severe varicella and zoster. *Vaccine* 2014 Jan 3;32(2):277-83.
36. Waye A, Jacobs P, Tan B. The impact of the universal infant varicella immunization strategy on Canadian varicella-related hospitalization rates. 2013 Oct 1;31(42):4744-8
37. Mi Salvadori, Société canadienne de pédiatrie, comité des maladies infectieuses et d'immunisation. La prévention de la varicelle : les recommandations à l'égard de la vaccination antivarielleuse systématique à deux doses chez les enfants. *Paediatr Child Health* 2014-fev.

38. Lopez AS, Guris D, Zimmerman L, Gladden L, Moore T, Haselow DT, et al. One dose of varicella vaccine does not prevent school outbreaks: is it time for a second dose? *Pediatrics* 2006 Jun;117(6):e1070-7.
39. Wang Z, Yang H, Li K, Zhang A, Feng Z, Seward JF, Bialek SR, Wang C. Single-dose varicella vaccine effectiveness in school settings in China. *Vaccine*. 2013 Aug 20;31(37):3834-8.
40. Shapiro ED, Vazquez M, Esposito D, Holabird N, Steinberg SP, Dziura J, LaRussa PS, Gershon AA. Effectiveness of 2 doses of varicella vaccine in children. *J Infect Dis*. 2011 Feb 1;203(3):312-5
41. Human vaccines & Immunotherapeutics. Landes Bioscience 2013 December; 9:12, 2499-2502.
42. Centers for Disease Control and Prevention (CDC). Evolution of varicella surveillance--selected states, 2000-2010. *MMWR Morb Mortal Wkly Rep*. 2012 Aug 17;61(32):609-12.
43. Klein NP, Fireman B, Yih WK, Lewis E, Kulldorff M, Ray P, et al. Measles-Mumps-Rubella-Varicella Combination Vaccine and the Risk of Febrile Seizures. *Pediatrics* 2010 Jul;126(1):e1-8
44. Gillet Y, Steri GC, Behre U, Arsène JP, Lanse X, Helm K, et al. Immunogenicity and safety of measles-mumps-rubella-varicella (MMRV) vaccine followed by one dose of varicella vaccine in children aged 15 months-2 years or 2-6 years primed with measles-mumps-rubella (MMR) vaccine. *Vaccine*. 2009 Jan 14;27(3):446-53
45. Streng A, Liese JG. Decline of varicella vaccination in German surveillance regions after recommendation of separate first-dose vaccination for varicella and measles-mumps-rubella. *Vaccine*. 2014 Feb 12;32(8):897-900.
46. Czajka H, Schuster V, Zepp F, Esposito S, Douha M, Willems P. A combined measles, mumps, rubella and varicella vaccine (Priorix-Tetra): immunogenicity and safety profile. *Vaccine* 2009 Nov 5;27(47):6504-11.
47. Cha SH, Shin SH, Lee TJ, Kim CH, Povey M, Kim HM, et al. Immunogenicity and safety of a tetravalent measles-mumps-rubella-varicella vaccine: an open-labeled, randomized trial in healthy Korean children. *Clin Exp Vaccine Res* 2014 Jan;3(1):91-9.
48. Shinefield HR, Black S, Kuter BJ. Varicella immunogenicity with 1- and 2-dose regimens of measles-mumps-rubella-varicella vaccine. *J Infect Dis* 2008 Mar 1;197 Suppl 2:S152-5.
49. Weinberg A, Levin MJ. VZV T cell-mediated immunity. *Curr Top Microbiol Immunol*. 2010;342:341-57
50. Kim KH. Herpes zoster vaccination. *Korean J Pain*. 2013 Jul;26(3):242-8.
51. Cohen JI. Herpes zoster. *N Engl J Med* 2013 Oct 31;369(18):1766-7.
52. Brisson M, Edmunds WJ. The cost-effectiveness of varicella vaccination in Canada. *Vaccine*. 2002 Jan 15;20(7-8):1113-25.

53. Poletti P, Melegaro A, Ajelli M, Del Fava E, Guzzetta G, Faustini L et al. Perspectives on the impact of varicella immunization on herpes zoster. A model-based evaluation from three European countries. *PLoS One*. 2013 Apr 17;8(4):e60732.
54. Leung J Harpaz R, Molinari NA, Jumaan A, Zhou F. Herpes zoster incidence among insured persons in the United States, 1993-2006: evaluation of impact of varicella vaccination. *Clin Infect Dis*. 2011 Feb 1;52(3):332-40.
55. Brisson M, Gay NJ, Edmunds WJ, Andrews NJ. Exposure to varicella boosts immunity to herpes-zoster: implications for mass vaccination against chickenpox. *Vaccine* 2002 Jun 7;20(19-20):2500-7.
56. Brisson M, Melkonyan G, Drolet M, De Serres G, Thibeault R, De Wals P. Modeling the impact of one- and two-dose varicella vaccination on the epidemiology of varicella and zoster. *Vaccine*. 2010 Apr 26;28(19):3385-97
57. Donahue JG, Kieke BA, Gargiullo PM, Jumaan AO, Berger NR, McCauley JS, et al. Herpes zoster and exposure to the varicella zoster virus in an era of varicella vaccination. *Am J Public Health*. 2010 Jun;100(6):1116-22.
58. Zhou F, Shefer A, Wenger J, Messonnier M, Wang LY, Lopez A, Moore M, Murphy TV, Cortese M, Rodewald L. Economic Evaluation of the Routine Childhood Immunization Program in the United States, 2009. *Pediatrics* 2014 Mar 3.
59. Ozaki T. Long-term clinical studies of varicella vaccine at a regional hospital in Japan and proposal for a varicella vaccination program. *Vaccine* 2013 Dec.9;31(51):6155-60
60. Soárez PC, Novaes HM, Sartori AM. Impact of methodology on the results of economic evaluations of varicella vaccination programs: is it important for decision-making? *Cad Saude Publica*. 2009;25 Suppl 3:S401-14.
61. Banz K, Iseli A, Aebi C, Brunner M, Schmutz AM, Heininger U. Economic evaluation of varicella vaccination in Swiss children and adolescents. *Hum Vacci*. 2009 Dec;5(12):847-57

Tableau I. Schémas thérapeutiques de la prophylaxie chez les patients à risque

Table I. Treatment schedule of chickenpox prophylaxis in at-risk patients

Types of patients	Prophylaxis	Source
Non-immunized patients who underwent hematopoietic stem cell transplantation	Oral acyclovir 200 mg/day until completion of the immunosuppressant treatment and up to one year after	14. Kawamura <i>et al.</i> (2014)
	Oral acyclovir 1,000 mg/day for 35 days following the hematopoietic stem cell transplantation Followed by oral valaciclovir 500 mg three times a week up to one year after the hematopoietic stem cell transplantation	19. Oshima <i>et al.</i> (2010)
Immunocompromised patients non-immunized after VZV exposure	Immunoglobulins (VariZIG® or Varitect®)	21. CDC guidelines (2013)
Seronegative pregnant women exposed to VZV	Immunoglobulins (VariZIG® or Varitect®)	23. Cohen <i>et al.</i> (2011)
Pregnant women who contracted chickenpox	Oral valaciclovir or IV acyclovir if severe chickenpox	27. Charlier <i>et al.</i> (2014)
Newborns whose mothers contracted chickenpox 5 days before to 2 days after giving birth	Immunoglobulins (VariZIG® or Varitect®)	21. CDC guidelines (2013)

Premature newborns <28 weeks of gestation and <1,000 g, irrespective of the immune status of the mother	Immunoglobulins (VariZIG® or Varitect®)	21. CDC guidelines (2013)
Premature newborns >28 weeks of gestation whose mother is seronegative	Immunoglobulins (VariZIG® or Varitect®)	21. CDC guidelines (2013)

Tableau II. Incidence de la fièvre selon les stades en fonction du type de vaccin utilisé
Table II. Incidence of fever according to stages depending on the type of vaccine used

	MMRV	MMR + V
Fever 0-14 days following vaccination		
All types of fever	59%	39%
Fever >39°C	12.3%	6.9%
Fever 0-42 days following vaccination		
All types of fever	65.2%	51.6%
Fever >39°C	17.1%	11.9%