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A new challenge for Europe: introducing a pediatric quadrivalent vaccine for measles, mumps, rubella, and varicella

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KEYWORDS

Measles-mumps-rubella-varicella; MMRV; Quadrivalent vaccine; Varicella

Summary

Background: Varicella is often considered to be a benign disease of childhood. In fact, varicella is associated with serious complications and mortality even among healthy individuals.

Discussion: Although the course of varicella can be uncomplicated, it can also be associated with serious complications such as pneumonia, fluid and electrolyte disturbances, skin and soft tissue infections and central nervous system disturbances. Worldwide studies have confirmed the high frequency of disease as well as the resultant morbidity, mortality and medical resource use. A quadrivalent vaccine is now available in certain countries to protect against measles, mumps, rubella and varicella (MMRV). Countries that have initiated routine vaccination programs have reported substantial reductions in morbidity and mortality as well as improved health outcomes. The MMRV vaccine facilitates coverage against all four diseases, and would be expected to improve compliance as well as coverage of varicella.

Conclusions: Universal vaccination programs with MMRV should be considered as a way to reduce the medical and economic impact of varicella. The MMRV vaccine provides a means to achieve universal coverage.

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Introduction

Varicella is a common childhood disease that is considered primarily an inconvenient but uncomplicated rite of passage. In reality, the seriousness of varicella should not be underestimated because complications, and even death, can occur in otherwise healthy children.^{1,2} Healthy children under 12 years of age account for almost 50% of fatalities.³

Varicella can have potentially devastating consequences such as pneumonia, fluid and electrolyte disturbances, skin and soft tissue infections and central nervous system disease.⁴⁻⁶ Although adults account for a much smaller percentage of cases, varicella-associated mortality and complication rates are even higher among adults, and have increased over time.^{3,6,7}

Symptomatic treatment and antiviral agents can be used to manage varicella, but have a limited effect on the disease course in normal children. Prevention rather than treatment has therefore been recommended as the optimal approach to the disease.^{4,8} Universal vaccination appears to be the best way to reduce the incidence of varicella,^{4,6,9} and achieving this will also protect those who are not eli-

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gible for vaccination, such as immunocompromised persons and infants.⁶

Sharp decreases in morbidity and mortality rates from varicella have been attributed to implementation of vaccination programs in the U.S.^{10,11} U.S. death records showed that during the 25 years (1970-1994) prior to introduction of the varicella vaccine in 1995, 90 deaths per year were reported, primarily among children (84%).⁶ More recently, 8 varicella-related deaths were described in the U.S. between January 2003 and June 2004.¹

A U.S. case-control study reported that 87% of vaccinated children had mild varicella compared with 45% of unvaccinated children ($p < 0.001$).⁹ A five-year survey found that the incidence of varicella and hospitalizations declined approximately 85% in three U.S. communities with high vaccination rates.¹¹ Analytical models designed for France and Germany found that complication rates and medical resource use decreased substantially with high rates of coverage.^{12,13} Despite this, varicella vaccination rates of approximately 85% are still being reported among 19- to 35-month old children, indicating that more widespread vaccination is necessary.^{11,14} Of even greater concern, some countries do not perceive varicella vaccination as a high priority despite the preponderance of evidence showing that it is a major public health issue.⁴

The need for universal vaccination to eradicate varicella means that a new quadrivalent measles, mumps, rubella, varicella (MMRV) vaccine may become a key factor to ensure the successful implementation of routine childhood varicella vaccination in European and other countries.^{10,15-17} This article will describe the epidemiology of varicella, its complications, the worldwide experience with vaccination programs, and the potential for the MMRV vaccine to facilitate universal coverage rates in Europe.

Epidemiology and clinical manifestations of varicella

The clinical course of varicella typically involves an incubation period of 8 to 21 days, followed by a phase during which fever and malaise occur. A rash then appears, characterized by macules, papules, vesicles, pustules, and scabs. After 7 to 14 days, shedding of crusts can be expected.^{18,19}

The prevalence of varicella throughout Europe is high, albeit variable. In France, between 1991 and 1995,^{4,20} varicella was associated with a complication rate of 2%.

Morbidity and mortality data among non-immune persons in France from 1990 to 1999 revealed death rates of 7, 104, and 5,345 per million cases depending on whether the patient was 1 to 4 years, 25 to 34 years, or older than 65 years of age.²¹ Age is a risk factor for varicella-related mortality, with mortality rates increasing sharply for patients over 20 years of age.⁶

Other data from Europe confirm this. Among 384,000 children in Italy, 20,513 cases were reported.²² Varicella-associated morbidity increased steadily for children 0 to 4 years in age over the study period (1961 through 1996). Seroprevalence rates in Germany have been reported as fairly consistent, with 760,000 new cases in 1999.^{23,24} Ten percent of cases occurred in persons 12 years of age or

older. Varicella-associated complications were reported in approximately 6% of all patients, with an average of 0.1 hospital days/case. The annual rate of varicella-associated hospitalizations was 4.1 per 100,000 persons in Spain in 1999-2000, resulting in over 11,000 hospitalizations.²⁵ In Catalonia, seroprevalence rates of 85% among 5 to 9 year olds and 92% among 10 to 14 year olds were described, with an annual hospitalization rate of 2.8 per 100,000 persons.^{25,26} An analysis of death certificates in England and Wales estimated that there were 826,881 reported cases of varicella from 1985 to 1997, and found a case fatality rate of 9.2 per 100,000 consultations.²⁷

In Australia, approximately 240,000 cases are reported each year, with 1500 varicella-related hospitalizations and 10 to 20 fatalities.^{28,29} A cross-sectional survey found that approximately 56% of children had varicella, while 42% had been vaccinated.³⁰ These data are consistent with European data showing a high seroprevalence, low to moderate vaccination rates, and a higher than might be expected rate of childhood hospitalizations and deaths due to varicella.

Complications of varicella in children can be severe

The course of varicella is not always mild and uncomplicated.² Complications may include pneumonia, fluid and electrolyte imbalances, central nervous system disorders, bacterial skin infections, and permanent scarring. The most serious complications include pneumonia, encephalitis, cerebellar ataxia, arthritis, and Guillain-Barré syndrome.³¹ Pneumonia is a common complication, as are some of the more easily managed complications such as skin and soft-tissue infections and fluid and electrolyte disturbances.⁵ Invasive group-A β -haemolytic streptococcal infection is also a risk in children with varicella.³² While rare, children developed serious complications such as necrotizing fasciitis, Reye's syndrome and encephalitis in the prevaccine era.

Congenital varicella syndrome is another rare yet very serious outcome of varicella infection. The affected infant typically experiences low birth weight, cutaneous scars, limb hypoplasia, and ocular and neurological lesions.³³ A prospective study conducted in Germany and the United Kingdom between 1980 and 1993 found nine cases of congenital varicella syndrome among 1373 women who had varicella during the first 36 weeks of gestation.³⁴ Only two of these cases occurred among 472 pregnancies in which maternal varicella occurred. The authors concluded that while the risk of congenital varicella syndrome was small, the sequelae were serious enough to make prenatal diagnosis valuable, and further suggested that prevention through vaccination would be a good option.

Finally, purpura fulminans is a life-threatening complication that can occur secondary to varicella.³⁵ It is characterized by cutaneous hemorrhage and necrosis caused by disseminated intravascular coagulation and vascular thrombosis.³⁵

The value of universal vaccination

Universal vaccination of young children, combined with immunization of unvaccinated adolescents, is expected to dramatically reduce both the number of cases of varicella and its complications.^{6,36} The U.S. experience has shown that since the varicella vaccine has been available, there have been fewer cases of varicella and fewer complications and hospitalizations. The effectiveness of the Oka/Merck varicella vaccine was shown in a case-control study of 339 cases from 20 pediatric practices.⁹ This study, conducted between March 1997 and June 2003, found that the vaccine was 97% effective against typical disease ($p < 0.001$) the first year after vaccination, and 84% effective ($p = 0.003$) in years 2 to 8 after vaccination, for an overall effectiveness of 87% ($p < 0.001$). Varicella was significantly more severe in unvaccinated children ($p < 0.001$). Among 122 "breakthrough" cases that occurred in vaccinated children, 106 (87%), had mild varicella, compared with 98 of 217 (45%) in unvaccinated children ($p < 0.001$).

The declining incidence of varicella in three U.S. communities (1995 to 2000) was documented in a population-based surveillance study (Figure 1).¹¹ During the study period, the number of varicella cases declined 71%, 84%, and 79% in each of the three communities, with vaccine coverage of 82%, 74%, and 84% respectively. Accordingly, hospitalizations declined from 2.7 to 4.2 per 100,000 population in 1995 to 1.5 per 100,000 in 2000. These real-life results illustrate how universal vaccination has reduced the incidence of varicella as well as hospitalization rates in the U.S.

The importance of vaccination against varicella has been recognized in studies worldwide that have highlighted the positive impact of vaccination on improved health outcomes and greater cost-effectiveness. A prospective study of 683 children in Spain found complications in 14.8% ($n = 101$) of the children, with 5 requiring hospitalization.³⁷ Minor complications increased the disease duration as well as the cost. Medical visits and prescription drugs (€32.5 per patient) accounted for the majority of the direct costs, while workdays missed accounted for the greatest indirect costs (€62.6 per patient). The authors conceded that vaccination costs could exceed the direct costs, but

concluded that universal vaccination was economical when indirect costs were taken into account.

A cost-benefit analysis based on an epidemiological model and a prospective observational study of 1832 cases in France demonstrated the value of combining varicella vaccination with measles-mumps-rubella (MMR) vaccination.¹² The highest rates of vaccination coverage were associated with the greatest benefits, including the lowest incidence of varicella and its complications and the greatest cost savings. The model showed that when 80% of children were vaccinated, both the vaccinated and non-vaccinated populations benefited. When 70% or fewer were vaccinated, the risk of complications increased, particularly among non-vaccinated adults, a population that has a higher risk of complications. When vaccination coverage was higher than 40%, a reduction in direct medical costs associated with varicella was observed for all parameters, with much greater savings when indirect costs were considered.

A model examining the economic value of routine varicella vaccination in Germany assessed the benefits, costs, and cost-effectiveness over a 30-year period.¹³ Assuming a coverage rate of 85% and a vaccine efficacy rate of 86%, routine childhood vaccination could prevent approximately 611,000 varicella cases and more than 4700 major complications each year in Germany. Average yearly cost savings were estimated at €51.3 million. The benefit-cost ratio was greatest for adolescent vaccination, but this approach provided inferior medical outcomes. The authors concluded that routine childhood varicella vaccination was a highly efficient and cost-saving strategy to decrease the burden of varicella.

An Australian cost-effectiveness study simulated direct costs and complications of varicella over a 30-year period.³⁸ This simulation found that the infant vaccination program was more cost-effective than adolescent or catch-up programs. An infant program could avert 4.4 million cases, 13,500 hospitalizations, and 30 deaths over 30 years. These results were relatively insensitive to coverage rates of 50% to 80%. These results are in line with European results, where universal infant vaccination would have a positive impact on costs, medical resource used, morbidity, and mortality.

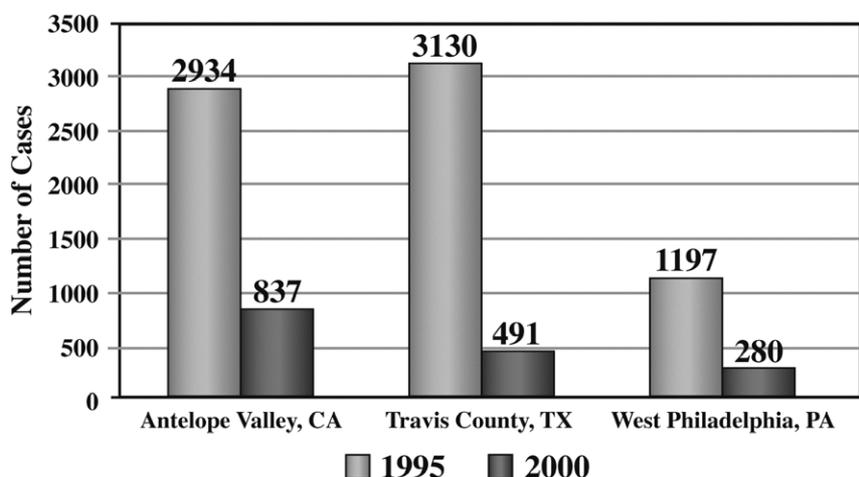


Figure 1 A population-based surveillance study demonstrated the declining incidence of varicella in three U.S. communities (1995-2000).¹¹

Assuming no impact of vaccination on Zoster, varicella vaccination was estimated to cost \$45,000, \$51,000, and \$18,000 per life-year gained from the health payer's perspective for infants, infants with catch-up campaigns, and preteen programs, respectively.³⁹ Mass infant varicella vaccination was estimated to be highly cost saving in Canada from a societal perspective. The cost-effectiveness of infant vaccination also will be influenced by the relationship between varicella and zoster, which is not known at this time

Barriers to vaccination

The goals of varicella immunization are to prevent the disease and its complications in children and especially in immunocompromised patients, pregnant women, and adults. Varicella vaccination has clearly decreased the number of varicella deaths in all age groups in the U.S. (Figure 2).⁴⁰ The estimated vaccination coverage in the U.S. has increased, but can the vaccine be even more widely used? A study examined records of 178,616 children (19 to 36 months old) to estimate varicella vaccine coverage in the U.S. between 1997 and 2004. Coverage rates increased from 26% in 1997 to 87% in 2004.⁴¹ Under-vaccinated populations included those living in the Midwest, living in a household with more than one child, living in a non-metropolitan area, living below the poverty line, having a mother who did not have a college degree, and having public providers; some of these factors were more important than others. The authors concluded that varicella vaccine uptake has been steadily improving, although additional opportunities exist for improved coverage.

An Australian study examined parental attitude to varicella vaccination programs.³⁰ The most common reasons parents gave for non-vaccination were that the child had previous varicella infection (34.5%), the parent was unaware of the vaccine (12.3%), the vaccine was not included in the schedule (11.7%), the cost of the vaccine was high (8.9%), they planned to get the child vaccinated but had not done so yet (7.2%), or that the vaccine was unavailable when other childhood immunizations were given (6.4%).

The most common reasons for non-vaccination in Italy included perceptions that varicella was a mild disease and that immunity obtained from childhood disease endures throughout adolescence and adulthood.⁴² There was a general misperception that breakthrough disease may be common following the vaccination. It was felt that stronger guidelines could address the need for varicella vaccination as a school entry requirement.

Attitudes towards varicella vaccine vary between countries. A recent survey conducted in France, Italy, and Germany examined physician ($n = 865$) and parental ($n = 3440$) attitudes towards varicella vaccination, to better understand why widespread vaccination is not practiced.⁴² While most physicians understood the seriousness of varicella, more than 80% of parents believed that varicella was harmless. Most German physicians advocated varicella vaccination in children (67.7%), compared with approximately 50% of French and 39% of Italian physicians. Physicians advocated for adolescent or adult vaccination in 63%, 23%, and 31% of cases, respectively, in Germany, France, and Italy. More than 80% of the time, parents followed physician vaccine recommendations. Sick-leave rates were 33% in Germany, 56% in France, and 74% in Italy. Only 22.5% to 36% of vaccinations were given concurrently with other vaccines, principally the MMR vaccine (60.8% to 88.3%). The authors theorized that acceptance could be enhanced by co-administration of varicella vaccine with MMR.

Physicians play a crucial role in the acceptance of any vaccination. As such, physicians must know that while the disease is often mild, there are severe complications that include death, morbidity and socio-economic consequences. Physicians in Europe are accustomed to concomitant administration of vaccinations, making concurrent administration of varicella with MMR a good way to go forward.

MMRV vaccine

Universal vaccination policies for varicella in the U.S. have led to a decline in disease when coverage exceeded 70%.⁴³ The continuation of existing vaccine policies is expected to lead to further reductions in varicella-associated mor-

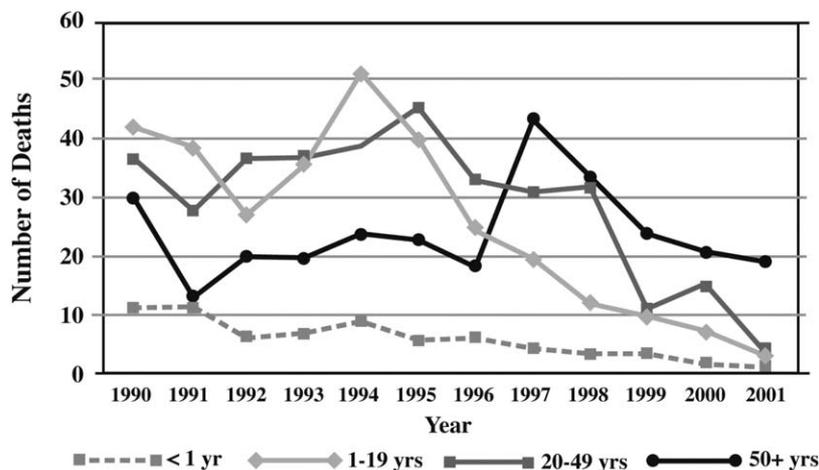


Figure 2 The number of varicella-related deaths has decreased in all age groups between 1990 and 2001, following the introduction of the vaccine in 1995.⁴⁰

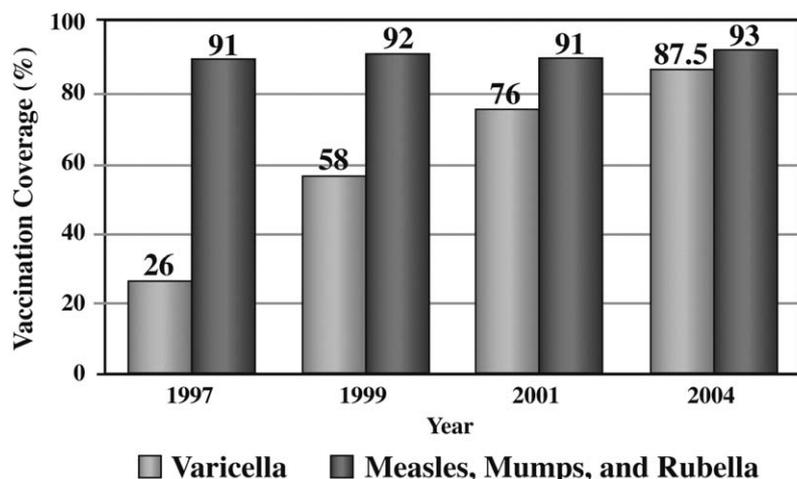


Figure 3 The estimated vaccination coverage in the U.S. is shown here. MMR coverage is greater than varicella coverage, suggesting that MMRV would serve to increase overall varicella immunization.⁴⁹

bidity and mortality.⁴³ A quadrivalent vaccine offers many benefits for implementing universal vaccination. Adding varicella to MMR decreases the number as well as the overall burden of injections. This decreased burden would be expected to enhance compliance and lead to increased rates of immunization. Most importantly, an effective, well tolerated quadrivalent vaccine for MMRV has the potential to achieve universal immunization (Figure 3).⁴

Efficacy and tolerability of MMRV

The Oka/Merck varicella vaccine is highly immunogenic and effective against clinical disease.⁴ The MMRV vaccine was studied in 812 children who were 12 months to 3.5 years old.⁴⁴ Children received either: (1) MMRV (ProQuad[®]) and placebo versus MMR (II) and varicella-zoster vaccine (Varivax[®]), or (2) diphtheria-tetanus-acellular pertussis vaccine and oral polio vaccine with MMRV or MMRII plus varicella-zoster vaccine. More than 95% of all children in this study seroconvert for measles, mumps, rubella and varicella, independent of the vaccine regimen.

An open label, multicenter study administered diphtheria-tetanus-acellular pertussis vaccine with combined *Haemophilus influenzae* type b conjugate-hepatitis B vaccines (Comvax[®]) plus either MMRV (ProQuad[®]) (concomitantly or 42 days later) or MMR (II) and varicella vaccination (Varivax[®]) (42 days later) to 1915 healthy children 12 to 15 months old.¹⁷ Concomitant administration of MMRV and the other vaccines was effective and well tolerated, with varicella antibody response rates of 89.7% to 98.9% of those achieved when the varicella vaccine was given alone. A potentially age-related lower antibody response to the pertussis vaccine was noted. A total of 76.9% to 80.6% of children in all groups experienced at least one systemic adverse event, with injection site adverse events being the most common. More injection site adverse events were noted among MMRV-vaccinated children who received concomitant administration of other vaccines as opposed to additional vaccination 42 days later. Patients who received MMRV reported a significantly higher incidence of fever than those who received MMR plus varicella, although most cases were mild and thought to be associated with concur-

rent conditions such as infection. The authors concluded that the results supported use of MMRV with the other childhood vaccinations.

In a prospective study conducted in the U.S., children 4 to 6 years old who had already received one dose of M-M-RII or M-M-RII plus Varivax were given MMRV (ProQuad[®]) with placebo, ($n = 399$), M-M-RII and placebo ($n=195$), or M-M-RII and Varivax[®] ($n = 205$).¹⁶ Noninferiority was demonstrated in antibody response to measles, mumps and rubella between children who received MMRV and children who received M-M-RII. The same was true for varicella antibody response in children receiving MMRV and Varivax. Postvaccination seropositivity rates for antibodies against all four viruses were approximately 100% in all cases. Small increases in measles, mumps and rubella antibody titers were observed. Injection site reactions were the most common adverse experiences, occurring in 51.3% to 56.2% of children in each group. Systemic adverse experiences occurred in 54.7% to 60% of children in each group. MMRV was thought to be appropriate in place of a second dose of M-M-RII or M-M-RII plus Varivax, resulting in good efficacy and tolerability.

A trial of 3928 healthy children 12-23 months of age demonstrated the consistency of three different lots of MMRV (ProQuad[®]) by evaluating the safety and immunogenicity following a single dose and comparing the response with a control group of children who received M-M-RII plus Varivax[®].⁴⁵ Immune responses were similar among children who received each of the 3 lots of MMRV, and between the MMRV and control groups. In addition, one-year antibody persistence rates were >95% for each lot of MMRV. A greater incidence of fever was observed with MMRV than the control group (39.1% vs. 33.1%, $p = 0.001$), although the overall incidence of adverse events was comparable. MMRV was felt to have comparable immunogenicity and tolerability to M-M-RII plus Varivax[®], with long-term persistence of antibodies expected.

A multicenter study randomized 480 healthy 12-23 month old children to receive either MMRV (ProQuad[®]) plus placebo and a second dose of MMRV (ProQuad[®]) 90 days later, or M-M-RII plus Varivax[®].⁴⁶ The safety and immunogenicity of each regimen was evaluated. Rash (5.9% vs.

1.9%) and fever (27.7% vs. 18.7%) were more commonly reported following the first dose of MMRV compared with M-M-RII plus Varivax; the incidence of other adverse events was similar between the two groups. Response rates >90% were observed to each vaccine in both groups. The geometric mean titers to measles and mumps were significantly higher following the first dose of MMRV compared with M-M-RII plus Varivax. The two treatments were considered to be similar in terms of both tolerability and immunogenicity.

Until recently, the majority of children in the U.S. received a single-dose of varicella vaccine. During an outbreak, the effectiveness of a single dose in children under 13 years old is approximately 95%, making it important to evaluate whether of a second dose might be of use, especially if the goal is to end endemic disease in the U.S.⁴⁷ The Advisory Committee for Immunization Practices in the U.S. has recently recommended that a second dose of varicella vaccine be administered at 4-6 years of age, the same time as the second dose of MMR vaccine, in order to increase the protection provided by the vaccine and decrease varicella outbreaks.⁴⁸

Conclusions

The complications of varicella can be severe. Universal vaccination can dramatically reduce the incidence of varicella, varicella-associated complications, hospitalization rates and fatalities. MMRV is an immunogenic and well tolerated vaccination that induces immune responses similarly to its component vaccines M-M-RII and Varivax and is compatible with other childhood vaccinations. As a quadrivalent vaccine, MMRV has the potential to improve compliance and coverage rates for varicella vaccination. Worldwide data are available to allow physicians and administrators to weigh the costs and benefits of vaccination. It is now a matter of public policy for each national government to determine how best to use MMRV to improve local health outcomes.

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Conflict of Interest statement

No competing interest declared.

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