Varicella Vaccination in Japan, South Korea, and Europe

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The most extensive use of varicella vaccine has been in the United States and Canada, where it is universally recommended. However, a number of other countries now have recommendations for use of the vaccine, which has been expanding in Europe and Latin America. In this article, we review information concerning varicella vaccination in Japan, where the vaccine was first developed, and in South Korea and parts of Europe. Despite the worldwide availability of an efficient vaccine, varicella vaccination policy is highly variable from country to country. The recent development of a tetravalent vaccine against measles, mumps, rubella, and varicella could modify this variability in the future. It is evident that efforts to control varicella will spread gradually to all continents.

Although varicella vaccine has been used for the universal vaccination (UV) of children in the United States since 1995, other countries have been slow to adopt it until recently. Even Japan, where the vaccine was developed, is far from universal immunization against varicella. Nevertheless, the use of varicella vaccine is accelerating, and, in this article, we review the policies in Japan, South Korea, and parts of Eastern and Western Europe.

JAPAN AND SOUTH KOREA

Takahashi et al. [1] developed a live attenuated varicella vaccine in Japan in 1974, using the Oka strain of varicella-zoster virus (VZV). The vaccine was well tolerated, immunogenic, and efficacious in both healthy and high-risk children in extensive clinical trials [2, 3]. In Japan, varicella vaccine is produced by the Research Foundation for Microbial Diseases (called "Biken" in Japan) at Osaka University, Osaka. Since 1987, the vaccine has been recommended for use in susceptible persons at $\geqslant$12 months of age. In addition, it is recommended for patients with acute leukemia, malignant tumors, nephrotic syndrome, and asthma when they are in remission and not severely immunosuppressed. Vaccination of health care workers who are susceptible is particularly recommended, as is vaccination of susceptible adults, individuals in closed communities, and siblings of immunosuppressed individuals. Contraindications to vaccination include acute febrile illness, pregnancy, and a history of anaphylaxis to vaccine components. Because varicella vaccination is not compulsory, coverage among infants has increased only from 6.8% at introduction in 1987 to 32.1% in 2005.

The low level of vaccine coverage among Japanese infants will not alter the circulation of wild-type VZV, and the epidemiology of natural varicella has not changed greatly since the introduction of the vaccine [4]. In the future, if the rate of vaccine coverage increases owing to the introduction of a compulsory immunization schedule, vaccine recipients will have a reduced risk of being exposed to VZV and, thus, reduced

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Table 1. Varicella epidemiology in the United States, compared with some European countries.

Country [reference(s)]	Varicella cases, no./100,000 persons/year	Average age of patients, years	Seroprevalence, % (age group, in years)	Hospitalizations, no./100,000 varicella cases/year	Deaths, no./100,000 varicella cases/year
United States [9][a]	1600	<4	…	4.1	…
Belgium [10, 11]	1200	…	93 (10)	3.4	0.8
France [12]	925	4	…	3.5	3.3
Germany [13–16]	915	…	94.2 (10–11)	6.7	0.7[b]
Italy [17]	200	4.5	82.1 (10–14)	0.18	…
Spain [18]	910	>5	90 (10–11)	2.7	3.7
The Netherlands [19]	254	…	>97.5 (10–14)	1.3	2
United Kingdom [20]	1291	…	95 (15)	4.5	4[c]

[a] Data are for the period before the start of the varicella vaccination program in 1995.
[b] Among patients <17 years of age.
[c] Among patients <25 years of age.

boosting of immunity via natural means. It is expected that a second vaccine dose will be required for maintaining protective immunity against natural disease.

The overall safety of the Biken vaccine has been good. However, in 1994, immediate anaphylactic or allergic reactions after many vaccinations became a big problem in Japan [5]. These reactions were associated with the use of gelatin as the stabilizer in the vaccine. Gelatin-free varicella vaccine was introduced in 1999, which resulted in a decrease in local reactions and skin rashes between days 0 and 2 after vaccination [6]. Antibody responses after immunization with gelatin-free vaccine, evaluated by immune-adherence hemagglutination assay and by ELISA using lectin affinity chromatography–purified glycoproteins from VZV, were similar to those after immunization with the previous, gelatin-containing vaccine [6].

Varicella vaccine has been distributed in South Korea since 1988. It was imported until 1993, when local manufacture began. There are no reliable statistics on vaccine coverage in South Korea, but the combined production volume is >500,000 doses annually, which is larger than the annual birth cohort of ~400,000. Since January 2005, varicella vaccination of children 12–15 months of age has been added to the national immunization recommendations, and, in July 2005, varicella became a designated (category II) infectious disease.

EUROPE

Varicella vaccination is not yet routine throughout Europe [7]. Each European country has its own health department and therefore its own health policy. Although the Oka strain–based vaccine (produced in Europe by Merck and GlaxoSmithKline) has been licensed in most countries, UV programs against varicella have been implemented only in Germany and Sicily. Other European countries remain reluctant to implement UV and recommend only vaccination targeted at certain high-risk groups, such as health care workers. This situation probably will be reconsidered with the commercialization of the tetravalent measles-mumps-rubella (MMR) with varicella (MMRV) vaccine (ProQuad by Merck and Priorix-Tetra by GlaxoSmithKline).

Epidemiology of varicella. Varicella usually is not a reportable disease in Europe, so an accurate estimate of disease burden is difficult to determine. The number of varicella cases could be underestimated significantly in some countries, as documented in Italy by Ciofi degli Atti et al. [8]. However, the epidemiology of varicella appears to be similar across Europe and even is similar to that in the prevaccine era in the United States (table 1) [9]. In both the United States and Europe, most people are infected before adolescence. Seroprevalence reaches ⩾90% by 10 years of age, and varicella incidence is ~13–16 cases/1000 people/year [9]. In most European countries, the highest incidence is observed among children 4–5 years of age, but more-complete and -standardized epidemiological studies are needed.

Economic burden. Several European studies have evaluated the impact of varicella vaccination, taking into account the direct as well as indirect costs of the disease [21]. However, economic structures and health policies vary quite considerably in Europe. In some countries where vaccination is free of charge, resources are not available for new vaccines. In countries where parents pay for vaccines, high coverage is difficult to attain. Although direct health care costs usually are supported by health departments, indirect costs, such as parents' work loss, are not. Thus, UV often fails to appear cost-effective when considered by health departments, even though it would be cost-effective from a societal perspective.

Vaccination policies. In 2004, the European Working Group on Varicella (Eurovar), created in 1998 to address varicella vaccination issues in Europe, published a consensus statement recommending "routine varicella vaccination for all healthy children between 12 and 18 months and to all suscep-

Table 2. Varicella vaccination status and recommendations in European countries.

Country	UV	Vaccination status and/or recommendation(s)
Austria	No	Recommended for high-risk groups: seronegative women of childbearing age; seronegative health care workers, teachers, or day care personnel; immunosuppressed children (upcoming chemotherapy or transplantation [administered before transplantation]); and seronegative family members of children at high risk
Belgium	No	On an individual, named-patient basis (vaccination not reimbursed): 1 dose for healthy children (1–24 months of age) or 2 doses (4–8 weeks apart) for older individuals Recommended for high-risk groups: seronegative women of childbearing age, seronegative susceptible adolescents and young adults, seronegative health care workers or persons with close contact with children, and seronegative family members of children at high risk
Cyprus	No	None
Czech Republic	No	Recommended for populations at high risk for complications
Estonia	No	Not yet recommended
Finland	No	On an individual, named-patient basis
France	No	Recommended for high-risk groups: seronegative medical students, paramedical students, health care workers, and persons with frequent contact with children; seronegative family members of immunosuppressed patients; and adults (>18 years of age) without previous VZV infection, after exposure
Germany	Yes	Recommended as part of the childhood vaccination schedule: 1 dose, at 11–14 months of age; 2 doses, at 15–23 months of age (if MMRV vaccine is administered) Recommended as catch-up vaccination for individuals ⩽17 years of age who do not have a history of varicella Recommended for the following seronegative individuals: staff in medical services and newly hired staff at facilities for preschool children, women attempting pregnancy, patients with severe neurodermatitis, patients with upcoming immunosuppressive therapy or organ transplantation, and susceptible persons in close contact with the above-mentioned groups
Greece	No	Routine vaccination recommended for healthy children 12–18 months of age and for susceptible children; not yet endorsed by the Ministry of Health
Hungary	No	On an individual, named-patient basis
Italy	Yes	Recommended to all susceptible adolescents and adults Recommended for universal pediatric vaccination if the region can ensure >80% coverage after 1 year[a]
Latvia	No	Recommended for children in accordance with indications in the vaccine's instructions for use and for susceptible adults
Lithuania	(Yes)	Recommendation for universal pediatric vaccination but not yet part of the vaccination schedule
Malta	No	Considering introduction of recommendations for childhood immunization, to be administered with the first dose of MMR vaccine
Poland	No	Recommended for susceptible children and adults and for patients with leukemia
Slovak Republic	No	Recommended for high-risk groups
Slovenia	No	Recommended for children in remission from acute leukemia, patients who need high doses of corticosteroids, health care workers, and healthy children if parents demand
Sweden	No	Recommended for high-risk groups and for seronegative healthy children >12 years of age and adults who have not had varicella
United Kingdom	No	Recommended for nonimmune health care workers and healthy close contacts of immunosuppressed patients On an individual, named-patient basis

NOTE. MMR, measles-mumps-rubella; MMRV, measles-mumps-rubella-varicella; UV, universal vaccination.

[a] So far, Sicily is the only region that has implemented this UV program.

tible children before their 13th birthday, in addition to catch-up vaccination in older children and adults without a reliable history of varicella and who are at risk of transmission and exposure" [22, p. 385]. The experts insisted that this policy should be recommended only if a very high coverage rate can be effectively achieved, to avoid any age shift in the epidemiology of chickenpox toward older children and adults [22]. This recommendation was in complete agreement with recommendations published by the World Health Organization (WHO) in 2003 [23].

Varicella vaccine has since been licensed in most European countries, but UV has been implemented in only Germany and Sicily. In Sicily, the vaccine is administered in the second year of life, and a catch-up vaccine is given at 12 years of age to those with no history of varicella. The situation in Germany is described in the subsection below. Elsewhere in Europe, policy varies from country to country (table 2). In general, vaccination is recommended for high-risk populations, such as health care workers, nonimmune adults, and nonimmune persons living with immunocompromised individuals. Since MMR vaccination is included in all European vaccine schedules and since good coverage usually is reached, varicella vaccination may be

regarded more favorably once the tetravalent MMRV vaccine is licensed. The experience in the United States suggests that optimal protection against VZV infection would be obtained best if 2 doses of varicella vaccine are given in early childhood. If a 2-dose schedule is adopted in Europe, it would be considered important to harmonize the doses with existing MMR schedules.

Concerns about UV. The European countries that have not yet recommended UV have various arguments for rejecting it. They mostly have yet to be convinced of the significance of the disease burden and of the cost-effectiveness of the vaccine, the duration of protection, and the impact of childhood vaccination on herpes zoster (HZ) epidemiology, since the theoretic possibility exists that decreased circulation of wild-type virus resulting from widespread vaccination will reduce opportunities for natural boosting of the immune response in the elderly and, therefore, will lead to an increase in cases of HZ. The economic issues discussed earlier are certainly a major barrier to the introduction of varicella vaccination in some countries.

Germany. Germany was the first European country to recommend UV against varicella. The vaccine was licensed in 1984 for use with patients at high risk for severe varicella, such as seronegative patients with acute leukemia, and their close contacts, as well as with health care workers in special hospitals. In 1994, when a vaccine formulation became available that could be stored in a refrigerator between 2°C and 8°C, the Standing Committee on Vaccinations (STIKO) at the Robert Koch Institute, Berlin (a German federal institution responsible for disease control and prevention), extended the recommendations to include healthy children $\leqslant$6 years of age and to seronegative women of childbearing age. Four years later, the recommendations were widened to include susceptible adolescents and adults. However, only a small number of individuals were vaccinated. In 2001, on the basis of seroprevalence data showing immunity gaps among adolescents [13], vaccination of adolescents 12–15 years of age who did not have a history of varicella was recommended [24]. The number of vaccinated individuals increased but still remained low. In 2001, STIKO also recommended that vaccination after exposure should be considered for persons without a history of varicella who were at risk for severe varicella, if the vaccine could be administered within 5 days of exposure or within 3 days after onset of lesions in the index case [24].

In July 2004, STIKO recommended UV, on the basis of evidence from epidemiological studies showing a continuing high disease burden of varicella among young children [14, 25] and of modeling that favored vaccination of all infants rather than the adolescent-vaccination strategy [15, 26], together with the success of the varicella vaccination program in the United States [27, 28]. Vaccination was scheduled for infants 11–14 months of age, preferably at the same time as administration of the MMR vaccine. Catch-up vaccination for other children and adolescents was recommended, particularly for persons 9–17 years of age who did not have a history of varicella [29]. Susceptible individuals >13 years of age had to receive 2 doses administered at least 4 weeks apart. Previous targeted indications also were retained (table 2). However, the indication for children with leukemia is currently being deleted because of the danger of vaccine complications.

The German childhood vaccination schedule implemented in July 2006 [30] recommends use of the tetravalent combination MMRV vaccine for infants and children. This MMRV formulation should be administered in a 2-dose regimen to all children (table 2). The second dose of MMRV vaccine should reduce the number of vaccinees with primary vaccine failure and should improve vaccine uptake. Monovalent varicella vaccines are to be used as before.

The implementation of UV in Germany was aimed mainly at reducing the high numbers of VZV infections, estimated at 750,000 cases/year [31]. Data on complications, hospitalization rates, and costs incurred by varicella also contributed to the rationale for implementing UV [14, 15]. Furthermore, the decision to implement UV was stimulated by the expectation that herd immunity would protect susceptible infants, young children, pregnant women, and immuncompromised individuals not eligible for vaccination from severe varicella. As with most other vaccinations recommended by STIKO, statutory health insurance covers the costs of UV. The number of vaccine doses sold increased in proportion to the degree that the statutory health insurance funds were paying for varicella vaccination. Sales figures for varicella vaccine rose from 27,000 doses in 2003 to 406,000 doses in 2005, and sales of 565,000 doses were estimated in 2006 (Intercontinental Marketing Services Health, Inc., unpublished data). Thus, it can be estimated that half of the birth cohort in 2006 was vaccinated. Increasing compliance with varicella vaccination can be expected if the combination MMRV vaccine is used. In 2004, coverage rates at school entry for the MMR vaccine were 93.3% for the first dose but only 67.7% for the second dose [32]. Therefore, much effort will be necessary to enhance vaccine uptake.

Varicella is not a notifiable disease in Germany. In 2005, a countrywide varicella sentinel surveillance network was initiated by the working group for measles and varicella, to collect valid epidemiological data for monitoring the implementation of the immunization program and its impact on disease epidemiology. This working group is a joint initiative of the Robert Koch Institute and the vaccine manufacturers. Data on frequency and distribution of varicella and HZ, the frequency of breakthrough disease, and the number of vaccine doses administered are generated by monthly sentinel questionnaires [32].

Eastern European countries. In Eastern Europe, the ca-

pacity for funding national vaccination programs is limited (table 2). Thus, UV is in fact recommended in Lithuania, but it cannot be incorporated into the national childhood immunization schedule because the vaccine is not funded by the state. Consequently, the vaccine is rarely administered.

The vaccine was registered in Latvia in 1997, but only 100 persons (of which 72 are <18 years of age) were vaccinated in 2005, owing to the high cost. Nevertheless, Latvian health authorities are discussing the introduction of infant varicella vaccination into the national vaccination schedule in 2008. In Estonia, the first varicella vaccine was registered in 1999, but it is not yet recommended officially.

Slovenia will reconsider a vaccination program when the MMRV vaccine is available. In the Czech Republic, there is ongoing discussion among clinicians and epidemiologists regarding the possibility of including the varicella vaccine in the general vaccination scheme, because the economic impact of the disease from loss of earnings by parents caring for children becomes a social problem in some instances. In the Slovak Republic, licensure of varicella vaccine was approved in 2007 for use with high-risk populations. In Poland, varicella vaccination is recommended only for high-risk groups and is publicly funded for these persons. In Hungary, the vaccine can be obtained for use on a case-by-case basis, in accordance with the manufacturer's instructions.

DISCUSSION

The type of varicella vaccine available worldwide contains the Oka strain of live attenuated VZV and was developed originally by Takahashi et al. [1] in Japan in 1974. Although Japan (in 1987) and South Korea (in 1988) were the first countries to license the vaccine and although >10 years have elapsed since the United States commenced successful UV of children, other countries have been slow to consider their varicella disease burden and to develop policies for use of the vaccine. Although the vaccine continues to be underutilized in Japan, countries such as South Korea, Canada, Brazil, Uruguay, Qatar, Taiwan, and Australia have adopted UV, as have Germany and Sicily. Some other European countries appear to be likely to do so once the combined MMRV vaccine is available to them. Other countries in Europe and elsewhere will be constrained by the vaccine's cost and most likely will be guided by the WHO recommendations published in 2003 [23], which state that "routine childhood immunization against varicella may be considered in countries where this disease is a relatively important public health and socioeconomic problem, where the vaccine is affordable, and where high (85%–90%) and sustained vaccine coverage can be achieved…the vaccine may be offered in any country to individual adolescents and adults without a history of varicella, in particular to those at increased risk of contracting or spreading the infection."

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