The Immunological Basis for Immunization Series

Module 10: *Varicella-zoster* virus

Immunization, Vaccines and Biologicals

World Health Organization

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Contents

Abbreviations and acronyms

ACV	acyclovir
CA	California (USA)
CDC	Centers for Disease Control (USA)
CMI	cell-mediated immune
CSF	cerebrospinal fluid
DNA	deoxyribonucleic acid
ELISA	enzyme-linked immunosorbent assay
FAMA	fluorescent antibody to membrane antigen
GMT	geometric mean titre
gpELISA	glycoprotein ELISA (test)
GSK	GlaxoSmithKline
HELF	human embryonic lung fibroblasts
Ig	immunoglobulin
MA	Massachusetts (USA)
MMR	measles-mumps-rubella (vaccine)
MMRV	measles-mumps-rubella-varicella (vaccine)
NY	New York (USA)
PA	Pennsylvania (USA)
PCR	polymerase chain reaction
PFU	plaque forming unit
SI	International System of Units
TA	Texas (USA)
TN	Tennessee (USA)
VZIG	varicella-zoster immune globulin
VZV	varicella-zoster virus
VZVIP	Varicella Zoster Virus Identification Program (USA)

Preface

This module is part of the Series "The Immunological Basis for Immunization", which was initially developed in 1993 as a set of eight modules focusing on the vaccines included in the Expanded Programme on Immunization (EPI) . In addition to a general immunology module, each of the seven other modules covered one of the vaccines recommended as part of the EPI programme, i.e. diphtheria, measles, pertussis, polio, tetanus, tuberculosis and yellow fever. These modules have become some of the most widely used documents in the field of immunization.

With the development of the Global Immunization Vision and Strategy (2005-2015) (http://www.who.int/vaccines-documents/DocsPDF05/GIVS_Final_EN.pdf) and the expansion of immunization programmes in general, as well as the large accumulation of new knowledge since 1993, the decision has been taken to update and extend this series.

The main purpose of the modules - which are published as separate disease/vaccine-specific modules - is to give immunization managers and vaccination professionals a brief and easily-understood overview of the scientific basis of vaccination, and also of the immunological basis for the WHO recommendations on vaccine use that since 1998 are published in the Vaccine Position Papers (*http://www.who.int/immunization/documents/positionpapers_intro/en/index.html*).

WHO would like to thank all the people who were involved in the development of the initial "Immunological Basis for Immunization" Series, as well as those involved in its updating, and the development of new modules.

[1] This programme was established in 1974 with the main aim of providing immunization for children in developing countries.

1. Varicella-zoster virus (VZV) and its diseases

The primary infection with VZV is varicella (chickenpox), and its secondary infection is zoster (shingles).During varicella, latent infection with VZV develops due to infection of neurons from the skin vesicles (1,2,3). Weeks to years later, in the setting of a decrease in the cell-mediated immune (CMI) response to VZV, reactivation of the virus may occur, resulting in clinical zoster (4). CMI to VZV may be compromised by ageing and/or illness and treatment, for example after cancer chemotherapy or transplantation. In places where varicella vaccine is not commonly used, varicella is usually a disease of children, and zoster a disease of adults.

VZV is a member of the herpesvirus family. It has 71 genes, all of which are expressed in lytic infection and seven of which are expressed in latent infection (5). Only neurons support latent infection. There is one serotype, but several genotypes are known, with small differences in their DNAs, classified as European, Japanese, and Mosaic (6). Recently, 3% of VZV strains circulating in the United States of America have been identified as Japanese type (7).

Diagnosis of VZV can best be made by demonstration of the virus in skin lesions, by polymerase chain reaction (PCR), immunofluorescence, or virus isolation in cell culture.Serologic reactions are mainly useful to indicate immunity or susceptibility to varicella (8).

Clinically chickenpox is manifested by fever, malaise, and a generalized vesicular rash that is especially concentrated on the head and trunk; the rash occurs in crops over five to six days. The self-limited illness is characteristically not severe, although there are a number of associated complications, which include bacterial superinfections (cellulitis, pneumonia, osteomyelitis), and neurological complications (cerebellar ataxia, encephalitis). Immunocompromised individuals are at increased risk to develop severe varicella, manifested by pneumonia, hepatitis, and an extensive skin rash (9). A rare but often severe congenital syndrome is associated with varicella acquired in utero due to maternal chickenpox. Babies with this syndrome commonly have abnormalities of the extremities, skin scarring, central nervous system-damage, frequent clinical zoster, and death in infancy. Newborn infants whose mothers have varicella at term, are at risk to develop severe varicella due to immaturity of their cell-mediated immunity (CMI) and absence of transplacental maternal antibodies (10).

Chickenpox is highly transmissible by the airborne route, with the infecting virus coming predominately from the vesicular skin lesions (3). Reported infection after household exposure ranges from 61%-100%. The incubation period ranges from 10-21 days.Second attacks of varicella are unusual, but have been reported (5). Boosting of immunity in immunes without disease following exposure to the virus has also been reported (5).

Zoster appears clinically as a unilateral vesicular skin rash in a dermatomal distribution.It may be painful, or pruritic, or both. Zoster is also contagious to others as chickenpox; it is however somewhat less contagious than varicella (5).

VZV infections may be treated with oral or intravenous acyclovir (ACV), which inhibits viral DNA synthesis. The intravenous route is usually reserved for severe infections in patients at high risk for significant morbidity or mortality. The newer drugs famciclovir and valacyclovir may also be used to treat zoster in adults (11,12).

2. Live attenuated varicella vaccine

VZV was successfully attenuated by Takahashi and colleagues in 1974, by serial passage of a clinical isolate from an otherwise healthy boy with chickenpox (13). Attenuation was achieved by passage 11 times at 34°C in human embryonic lung fibroblasts (HELF), 12 passages at 37°C in guinea-pig fibroblasts, and 5 to 6 passages in MRC -5 human fibroblasts at 37°C. Infected cell suspensions were sonicated to obtain cell-free VZV.Standard safety-testing after injection into small mammals was also performed, and did not identify any adventitious agents. Varicella vaccines contain a mixture of Oka and parental strains (14-16). Sequencing of the Dumas strain of wild-type VZV, and the Oka strain, has shown that there are 42 differing bases, over one third of which are in gene 62.Three fixed mutations have been identified in Oka strains present in skin rashes of vaccinees, all located in gene 62 (15,17,18). Although the genetic basis for attenuation is still unknown, it is possible to differentiate Oka from wild-type VZV by PCR in clinical specimens (8).

Monovalent varicella vaccine is produced in the United States (VarivaxTM; Merck & Co., Inc.), the Kingdom of Belgium (VarilrixTM; GlaxoSmithKline), and Japan (OKAVAX™; Biken, distributed by Aventis Pasteur). These vaccines vary slightly in passage number in human diploid cells, antibiotics for sterility, stabilizers and minor constituents. Each preparation guarantees 1350 plaque forming units (PFU) per 0.5 ml at expiration; doses at release vary from 3 000 to 17 000 PFU. Combination vaccines for measles-mumps-rubella-varicella (MMRV) are produced by Merck (ProQuadTM)and GSK (Priorix-TetraTM). MMRV vaccines are licensed for children 12 months to 12 years old. They contain the same measles-mumps-rubella (MMR) components as MMR vaccine, but have a higher concentration of Oka varicella vaccine (~ 10 000 PFU at expiration) than monovalent varicella vaccines. A formulation of the Oka strain containing~ 17 000 PFU (ZostavaxTM), is used for prevention of zoster when administered to healthy adults above the age of 60 years.

3. Immunity to varicella

Traditionally, for a number of reasons, immunity to VZV after disease or immunization is assessed by measuring antibody titres. It was assumed for years that neutralizing antibodies played a major role in long-term protection against this virus. In addition, the role of CMI in host defence against this intracellular pathogen went unrecognized until the 1980s.It is more difficult, complicated, and expensive to measure CMI to VZV than to measure antibody titres. It is now appreciated that although antibodies can neutralize extracellular virus, CD4 and CD8 T lymphocytes are critical in defence against the intracellular forms of VZV, the major means by which the virus spreads in the body during acute illness. Varicella can be prevented or modified by administering pre-formed antibodies by giving varicella-zoster immune globulin (VZIG) or VariZIG within the first three days after infection has occurred. At that time VZV is probably multiplying mainly in the tonsils (19), where in the superficial layer of the stratified epithelium, cell-free virus can potentially be formed, as in the superficial epidermis of the skin (3). After that time, until the virus reaches the skin in vesicular lesions, spread is accomplished mainly by the intracellular route, requiring CMI for host defence. It is possible that neutralizing antibodies can prevent a second infection with VZV after an immune individual is exposed to the virus, by interfering with early replication which produces cell-free virus. Antibodies are most often measured by enzyme-linked immunosorbent assays (ELISAs), or by fluorescent antibody to membrane antigen (FAMA) assays, which are described below.

Cellular immunity plays a crucial role in defending the infected person from spread of the virus. This phenomenon was first recognized clinically, when patients with congenital absence of cellular immunity died from uncontrolled spread in the body of VZV during varicella. By contrast, severe or fatal varicella was not recognized in children with isolated agammaglobulinemia. Children with low CMI due to cancer or transplantation were later recognized to be at risk of developing severe or even fatal varicella (20).Administration of VZIG soon after infection probably enables the altered host to neutralize extracellular virus early in infection, thereby lowering early VZV multiplication and the eventual viral load.

Cellular immunity, not humoral, protects persons with latent VZV from developing zoster. This may indicate the cell-associated nature of spread of the virus to skin from reactivation in neurons. Low CMI to VZV is a necessary but not sufficient setting for zoster; most individuals with low CMI to VZV do not develop zoster. Probably zoster results from a two-step process, reactivation of the latent virus (due to factors that remain unknown), and decreased CMI, disabling control of the pathogen and development of symptoms. Because patients with isolated defects in antibody synthesis also do not develop recurrent chickenpox, CMI may thus also participate in prevention of reinfection with VZV. Undoubtedly redundancy in the system affords better protection, and thus may have evolved in this fashion.

4. Techniques useful to measure antibodies and cell-mediated immune (CMI) to varicella-zoster virus (VZV)

The first available practical test to measure VZV antibodies was by the complement fixation assay (21). This test was useful to measure antibodies in acute and convalescent sera but was not sensitive enough to identify persons with immunity to chickenpox. The FAMA assay was developed in the early 1970s as a means to discriminate between persons who are susceptible and those who are immune to varicella (22). It remains the "gold standard" for this determination (8). Considerable past experience with this assay indicates that ≤3% of individuals contract varicella after a household exposure to VZV, if their titre by FAMA is ≥1:4. By contrast, unvaccinated individuals who have FAMA titres of ≤1:4 have a roughly 75% chance of developing chickenpox after a household exposure (23). The FAMA assay measures antibodies to glycoproteins of VZV that are present on the surface of tissue culture cells (human embryonic lung fibroblasts) infected with VZV. The infected cells are unfixed, which is thought to preserve the natural conformation of the viral antigens, and account for the high degree of accuracy with this assay. In addition to the data on protection mentioned above, approximately 1000 individuals with no antibodies to VZV prior to varicella or on day one of illness, were demonstrated to seroconvert with this test following development of chickenpox (24, 25).

Experience with the use of FAMA as a predictor of varicella disease protection after household exposure

	FAMA seronegative	FAMA seropositive
Ampofo K et al., Clin. Infect. Dis. 2002; 34(6): 774-9.	17/37 (46%)*	2/50 (4%)*
LaRussa PS et al., J. Infect. Dis. 1985; 152(5): 869-75.	5/7 (71%)	0/15 (0%)
Gershon A et al., J. Infect. Dis. 1990; 161(4): 661-6.	—	0/38 (0%)
Williams et al., J. Infect. Dis. 1974; 130(6): 669-72.	3/3 (100%)	0/11 (0%)
Gershon A and S Krugman, Pediatrics 1975; 56(6): 1005-8.	12/16 (75%)	0/7 (0%)
Unpublished lab diagnostics	3/5 (60%)	0/10 (0%)
TOTAL	40/68 (59%)	2/131 (2%)

* Vaccinees

Another serologic test that has been developed is the glycoprotein (gp)ELISA test, which has been used extensively to evaluate responses to varicella vaccine. This test utilizes glycoproteins of VZV that are coated on 96 well ELISA plates. This assay was developed and is performed exclusively by Merck and Co. Although the gpELISA test is useful to measure increases in titre of VZV antibodies, it yields false-positive results, particularly when used to identify low levels of antibodies, impairing its ability to demonstrate a reliable correlate of immunity (26,27,28). In a comparison of FAMA to gpELISA titres in vaccinated adults who eventually developed breakthrough varicella, all had FAMA titres of $\leq$1:4 in the year prior to varicella, but 2/17 (24%) had positive gpELISA tests, >5U/mL in these same sera (Gershon et al, unpublished). Similar results were reported in a comparison by investigators at Merck (28). In this series, 41 patients had levels of VZV antibodies considered moderately high by gpELISA, but only 40% had positive FAMA titres (>1:5). Of 16 patients with gpELISA antibody levels considered high, only 94% had positive FAMA values.

5. Protective antibody responses

As noted above, it has been well documented that individuals with a FAMA titre of >1:4 are highly unlikely to develop varicella after exposure. This is complicated, however, by the observation that second attacks of varicella can occur after the first illness. The incidence and pathogenesis of second attacks is unknown, but the phenomenon is thought to be rare, or unusual, in non-immunocompromised patients (29,30.31,32). One hypothesis is that low avidity of VZV antibody may be involved in permitting reinfection to occur, despite the presence of humoral immunity (31).

While the gpELISA has been proposed as an approximate indication of protection, it has not been validated, as has FAMA, in clinical situations in which individual vaccinees with titres considered negative or positive have been evaluated for protection after close exposure to VZV.

In general, persons with a positive titre in a commercial ELISA assay, are thought to be protected from varicella. Most naturally-infected individuals who have a positive ELISA titre also have a positive FAMA titre (33). In another study, using ELISA kits obtained from a different manufacturer however, 10% of individuals tested with positive ELISA tests had FAMA titres that were ≤1:4, indicating 10% false-positive reactions with this commercial assay (34). Commercial ELISA assays have not been useful to identify vaccine-induced immunity.

6. Vaccine efficacy and effectiveness

Two double-blind placebo-controlled studies of varicella vaccine in healthy children have been reported, one in the early 1980s with Merck's Oka vaccine (35), and the other (in the Republic of Finland) with monovalent Oka vaccine produced by GSK. In the Merck study, 468 children were immunized with one dose of varicella vaccine containing approximately 17 000 PFU. There were 446 children in the placebo group. During a nine-month follow-up, 39 cases of varicella occurred, all in the placebo group. The vaccineefficacy was therefore 100%. During a second year of follow-up, one vaccinee developed very mild varicella, with a resulting efficacy of 98%. It was estimated that seven years later, 95% of the vaccinees had remained free of varicella (36). A significant criticism of this study, however, is that the dose of vaccine used was about 6 to 12 times that in the currently licensed vaccine.

The Finnish study included 513 healthy children between one and three years of age who received three different GSK products; a high-dose vaccine (10 000 or 15 850 PFU); a low dose vaccine (630 or 1260 PFU), and a placebo. A seroconversion rate approaching 100% was found in vaccinees using FAMA. During a period of approximately two years, 65 cases of varicella were confirmed. Five were in the high-dose group (3% attack rate, efficacy 88%); 19 in the low-dose group (11% attack rate, efficacy 55%), and 41 (26% attack rate) in the placebo group (37). Neither this Merck vaccine nor the GSK vaccine doses are similar to the dose of virus in the licensed Merck vaccine, so it is difficult to make a comparison with the record of vaccine effectiveness in the United States. Both randomized, blinded studies however, indicate that varicella vaccination confers significant protection against clinical disease in healthy children, and thus represent proof of concept.

One dose of Merck's monovalent varicella (1350 PFU) was approved in 1995 for universal immunization of infants and children between the ages of one and two years in the United States, and since that time there has been a significant decrease in the incidence of varicella. In three sentinel counties in Texas (TX), California (CA), and Pennsylvania (PA), in the United States, in which active surveillance was carried out, there was an 80% decrease in varicella among vaccinated and unvaccinated residents between 1995 and 2003, indicating both personal and herd immunity (38). A study utilizing a database of cases of varicella in Massachusetts (MA) showed a similar decrease in chickenpox. There was also an 88% decrease in the incidence of hospitalizations due to varicella in children (39). Finally, a decrease in mortality of 88% from varicella was recorded between 1995 and 2003. Most of this decrease occurred in children between the ages of one to four years (40).

Published data regarding seroconversions after immunization have suggested that the effectiveness of varicella vaccine should be at least 90%. Most seroconversion rates after one dose of vaccine in infants and young children, using the gpELISA assay, were in the order of 95%. An early clinical trial involving 2475 children aged between one and 12 years, given 1000-1625 PFUs, reported a seroconversion rate of 96%, although the value considered to represent a positive titre was not given (41). More recent studies, using a value of >5gpELISA units/mL to indicate a positive response, reported seroconversion rates ranging from 86% to 96%, with most being greater than 90% (42,43,44).

Although, as described above, varicella vaccine has been highly successful in the United States, the incidence of the disease has not fallen significantly since the year 2000. Many outbreaks of varicella in highly vaccinated children in day care and schools, moreover, have indicated vaccine effectiveness of 80%-85% after a single dose of vaccine, rather than the anticipated 90%-95% effectiveness based on seroconversion data (45-55).Similarly, a case-control study of the use of varicella vaccine in clinical practice indicated effectiveness of about 85%, between years two and eight after vaccination (56, 57).

In order to investigate the possibility of primary vaccine failure after one dose of vaccine, the antibody responses of 148 infants immunized in New York (NY), Tennessee (TN), and California were examined, using the FAMA assay. A seroconversion against VZV was found in 76% (113/148) (23). These children were immunized in three different locations, so that it is not likely that improper storage of the vaccine was the cause of the problem. This degree of primary vaccine failure was unexpected, but it is consistent with the observed outbreaks of varicella among immunized children, and the already mentioned case-control study of the effectiveness of the vaccine over time (56, 57).

These serologic data suggest that there is significant primary vaccine failure after one dose of varicella vaccine (23). These children were on average one year of age when immunized, and sera from before and after (from one to six months) immunization were studied. The seroconversion rate three months after immunization was significantly higher than the seroconversion rate six months after vaccination, suggesting that some children who seroconverted initially lost detectable antibodies within a few months. In all probability, absence of FAMA antibodies in some vaccinees still results in some residual immunity due to CMI. This could explain why many children with breakthrough varicella have very mild infections. In a recent study of breakthrough varicella, in which the number of skin lesions were actually counted, 27% of the children had more than 50 skin lesions however, suggesting that a significant number of children with breakthrough disease may not have modified infections (58).

Waning immunity or secondary vaccine failure has also been proposed as the cause of breakthrough varicella in children immunized with one dose of vaccine. In a study in Antelope County, CA, conducted by the Centers for Disease Control (CDC), in which active surveillance of varicella was carried out, the clinical criterion of over 50 skin lesions was defined to indicate moderate to severe varicella. The rate of mild breakthrough disease was 82% between 1995 and 1998, but fell to 69% between 2001 and 2004 ($p \leq .001$). This decrease was hypothesized to be due to secondary vaccine failure or waning immunity. In addition, the incidence of breakthrough varicella increased about 10-fold between 1995 and 2003, and this was also attributed to secondary vaccine failure (59). In a case-control study of the effectiveness of varicella vaccine in clinical practice, however, a decrease in effectiveness was not observed, except during the first year after vaccination, when the effectiveness was 97%. After that time, effectiveness reached a plateau at about 85%, between years two to eight after vaccination (56, 57). It seems more likely therefore that the increase in breakthrough varicella over time in the CDC study was due to the accumulation of susceptibles due to primary vaccine failure rather than to waning immunity. No serologic studies were performed in the CDC study.

Because of the school outbreaks, continued transmission of wild-type VZV from vaccinees to others, evidence of primary vaccine failure after one dose, and possible waning immunity in some children, a second dose of varicella vaccine for all children was recommended by the CDC in June 2006 (60).

7. Persistence of antibodies after vaccination

There appears to be excellent persistence of antibodies in vaccinees, although most of these data were collected in an era when the wild-type virus continued to circulate and provided potential boosting of immune responses. In addition, for studies using gpELISA, the data are difficult to interpret because the end-point indicator for positivity was increased (from >0.3 units/mL to >5 units/mL) over a roughly 10-year period. In Japan, VZV antibodies were determined five years after vaccination of 26 healthy children; all had detectable neutralizing antibodies, and 96% had positive FAMA titres (61). Subsequent 10- and 20-year follow-up studies demonstrated that 100% of 25 young adults immunized as children remained seropositive by FAMA, and also had positive skin tests for CMI to VZV (62,63,64). An American study using vaccine at a potency similar to the licensed American product, revealed that of 214 vaccinees, 95% remained seropositive by gpELISA (>0.3 units/mL) up to six years after immunization (65). A subsequent study of 419 children showed that 414 (99%) remained seropositive (GMT 26 units/mL) after a similar interval (66). In roughly 500 additional healthy American children immunized in various clinical trials, and tested as long as six years later, over 95% were reported to be seropositive by gp ELISA(>0.4 units/mL) (36,67,68). In another group of 603 vaccinated children, there was greater than 89% persistence of gpELISA antibodies six years after vaccination (>0.6 units/mL) (69). In a study of 53 vaccinated American children whose antibody titres were measured by a modified FAMA test, most remained VZV antibody-positive 10 years after immunization, although about 20% of these children developed breakthrough illness (70). It is of interest that despite the high degree of persistence of VZV antibodies by gpELISA, the effectiveness of the vaccine is about 80%-85%.

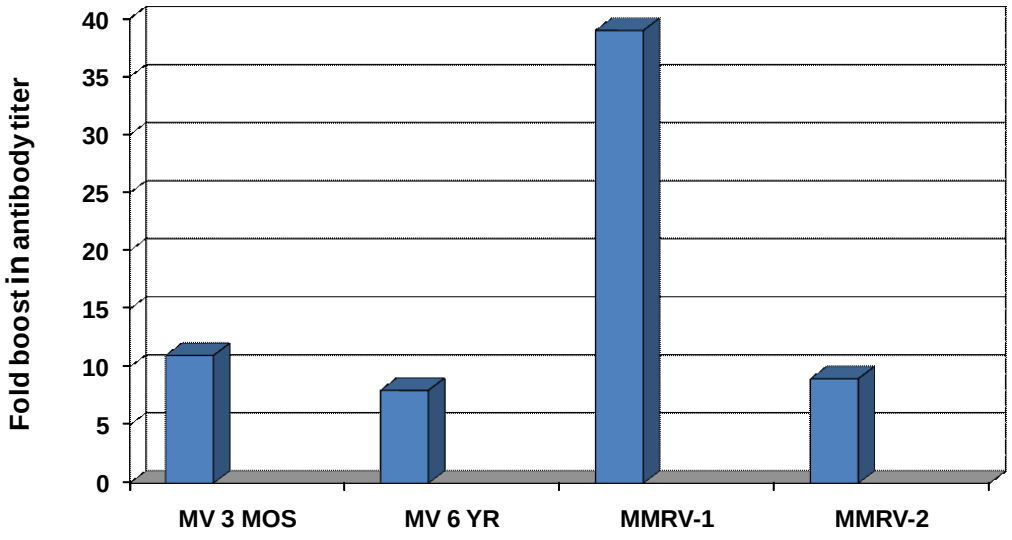
In contrast to children, humoral immune responses against VZV measured by FAMA appear to be less durable in adults than in immunized healthy children, despite two doses having been given to most ofthe adults (34,71).

There is little information on persistence of CMI to VZV after immunization. One study, however, indicated that in a group of 419 children, all had positive CMI determinations (average stimulation index 40; a value of five is considered positive) six years after immunization (66). Another study of 39 children revealed an average stimulation index of 9 (+1.4) one year after immunization (72).

Two doses of monovalent varicella vaccine were used in early clinical trials in leukaemic children and also in adults, due to a high incidence of failure to seroconvert by FAMA after one dose, and also due to rapid loss of VZV antibodies after vaccination in these groups. Adolescents had seroconversion rates of 75% after one dose (by gpELISA), a lower seroconversion rate than in children, leading to the recommendation that adults and adolescents be given routinely two doses of vaccine (41). Healthy children who had not yet reached their thirteenth birthday, however, were recommended to receive one dose, at least four months apart (73).

There are a few clinical trials, however, in which two doses of monovalent varicella vaccine were administered to children. The interval between the first and second doses ranged from several months to as long as six years. Data regarding humoral immune responses were all gpELISA determinations. Despite the aforementioned problems with this test, due to the comparisons being made in these studies, the results seem to provide useful information. It was universally noted that the seroconversion rate increased after two doses in comparison to one dose, and that the geometric mean titre (GMT) increased as well, no matter what the interval between doses (Figure 1). It has been hypothesized that the dramatic boosting of the immune response indicates that the primary immune response after one dose of vaccine was inadequate. In order to achieve a long-lasting protective response, two doses may be required. The specific data on immune responses after one and two doses of varicella vaccine are discussed below.

Figure 1: Booster response after dose



Increases in humoral immunity after a second dose of live Oka varicella vaccine reported in 4 studies. Boosts of 11-fold (n = 39; booster after 3 months) and 8-fold (n = 219; booster after 6 years), were recorded 6 weeks after monovalent (MV) Merck vaccine. Three months after a second dose, boosts of 39-fold (n = 381) after Merck vaccine (MMRV-1) and 9-fold (n = 48) after GSK vaccine (MMRV-2) were found. Different antibody tests were used for evaluation of each vaccine (see text).

After one dose of VarivaxTM in vaccinees, the seroconversion rate, using >5 gpELISA units/mL to indicate a positive response, was 87.3% with a GMT of 12.8 gpELISA units/mL (43). In this study, 1017 vaccinees received a second dose of varicella vaccine three months after the first dose. After the second dose, the seroconversion rate increased to 99.5% and the GMT to 141.5 gpELISA units/mL, indicating a marked booster response following the second dose (Figure 1).

In another study of 79 children given a second dose three months after the first, the GMT increased by a factor of 13 six weeks after the second dose, but one year later the GMTs were similar whether one or two doses had been given (74). In another study, 419 children were given a second dose six years after the first. Their GMT of antibodies to VZV measured by gpELISA three months later, increased 8-fold, from 26 to 219 units/mL (66).

Cellular immunity also increases after a second dose of varicalla vaccine. In one study, 39 healthy children received one dose of varicella vaccine, and 39 were given two doses three months apart. The mean VZV SI (International System of Units) one year after one dose was 9.3 (+ 1.3) and after two doses was 22.2 (+ 6.42) (72). In another study, a second dose was given three months after the first to 49 healthy children. Prior to receipt of the second dose, the mean VZV SI was 42 (+ 7), and three months later it was 63 (+ 9) (74).

Boosting of VZV antibody responses may be even greater when the combination vaccine measles-mumps-rubella-varicella (MMRV) is used as both the primary and secondary immunogen compared to the monovalent varicella vaccine. Antibody responses against all four virus components with the formulation containing 10 000 PFU of VZV revealed that, for the VZV component, 339/381 (89%) of children seroconverted by gpELISA, with a GMT of 12 gpELISA units/mL after one dose of MMRV. After a second dose three months later, the seroconversion rate was 99%, and the GMT was 469 gpELISA units/mL. In this study, the end-point for immunity was >5 gpELISA units/mL. The antibody levels against VZV increased by a factor of almost 40 after the second dose. By contrast, antibody levels to the MMR components increased by only a factor of two (75).In another study involving 799 children who had received monovalent varicella vaccine several years previously, GMTs by gpELISA increased by a factor of 12 after receiving MMRV, compared to an increase of eight times after receiving a second dose of Varivax™ (76).

In evaluating the MMRV vaccine produced by GSK (Priorix-Tetra), antibody titres to VZV immunoglobulin (IgG) were determined by indirect immunofluorescence (manufactured by Virgo) in 371 children. The seroconversion rate after two doses 6-8 weeks apart was 100% (77). As with other licensed MMRV vaccines, there were excellent responses to the MMR component. Following a second dose of either MMRV or monovalent varicella vaccine, the VZV GMT achieved was about 32 times higher with MMRV (4932µ/mL), compared with monovalent varicella vaccine (155µ/mL) (77). In another study of GSK vaccine, an ELISA assay from Behring was used in children who were first given either MMRV (n = 48)or MMR plus V (n = 45) as a first immunizing dose to evaluate VZV titres. Three to four years later, a dose of MMRV was given to all.Children who had received two doses of MMRV had GMTs that were nine times greater than those who received monovalent varicella vaccine followed by MMRV. Thus, although the antibody tests are different,

the vaccines made by different companies, and the vaccines deployed in slightly different ways, it appears that MMRV may be more immunogenic than monovalent varicella vaccine.

There are few data indicating the efficacy of two doses of varicella vaccine compared with one for infants and children. The one study available, however, strongly suggests that there will be better control of varicella if two doses of vaccine are given rather than a single dose. In the mid 1990s, 2216 healthy children aged between one and 12 years were randomized to receive one or two doses of varicella vaccine (five different lots of vaccine ranging in potency from 2900 to 9000 PFUs) three months apart. This study showed the projected efficacy of one versus two doses of varicella vaccine to be 94.4% versus 98.3% ($P \leq 0.001$) (43). Following household exposures, efficacy of one dose was 90.2% versus 96.4% for two doses. As yet, however, there are no efficacy data available for any formulation of MMRV.

8. Safety

Varicella vaccines have proven to be extremely safe, and the Merck vaccine alone has been administered to over 50 million children worldwide. A recent review of safety data submitted to Merck under the Varicella Zoster Virus Identification Program(VZVIP), indicated only rare serious adverse reactions - there were 3.4 reports to Merck per 10 000 doses of vaccine distributed. Vesicular rashes were the most commonly reported adverse event. Rashes that occurred within the first two weeks after vaccination were usually identified by polymerase chain reaction (PCR) as due to wild-type VZV, while rashes that occurred 15 to 42 days after vaccination were usually identified as Oka strain.Breakthrough varicella that occurred at least two months after vaccination were caused by wild-type virus. Of almost 700 reports of clinical zoster, VZV was identified in about 15%; Oka strain was identified in 57 children, and adults and wild-type virus in 38. No serious neurologic adverse events were associated with the immunization. Transmission of the vaccine strain was shown in five susceptible individuals with intimate exposure to a vaccinee, and each transmitting vaccinee had a vaccine-associated rash (5). Disseminated Oka VZV was identified in seven immunocompromised individuals, immunized accidentally, who developed rashes, pneumonia, and/or neurologic symptoms after vaccination. All responded to antiviral therapy (78). A similar experience was reported from data collected at the CDC.They also reported two children with zoster and meningitis who had Oka VZV detected in their cerebrospinal fluid (CSF). One child had received chemotherapy for cancer. Both recovered after antiviral therapy (79).

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The World Health Organization has provided technical support to its Member States in the field of vaccine-preventable diseases since 1975. The office carrying out this function at WHO headquarters is the Department of Immunization, Vaccines and Biologicals (IVB).

IVB's mission is the achievement of a world in which all people at risk are protected against vaccine-preventable diseases. The Department covers a range of activities including research and development, standard-setting, vaccine regulation and quality, vaccine supply and immunization financing, and immunization system strengthening.

These activities are carried out by three technical units: the Initiative for Vaccine Research; the Quality, Safety and Standards team; and the Expanded Programme on Immunization.

The Initiative for Vaccine Research guides, facilitates and provides a vision for worldwide vaccine and immunization technology research and development efforts. It focuses on current and emerging diseases of global public health importance, including pandemic influenza. Its main activities cover: i) research and development of key candidate vaccines; ii) implementation research to promote evidence-based decision-making on the early introduction of new vaccines; and iii) promotion of the development, evaluation and future availability of HIV, tuberculosis and malaria vaccines.

The Quality, Safety and Standards team focuses on supporting the use of vaccines, other biological products and immunization-related equipment that meet current international norms and standards of quality and safety. Activities cover: i) setting norms and standards and establishing reference preparation materials; ii) ensuring the use of quality vaccines and immunization equipment through prequalification activities and strengthening national regulatory authorities; and iii) monitoring, assessing and responding to immunization safety issues of global concern.

The Expanded Programme on Immunization focuses on maximizing access to high quality immunization services, accelerating disease control and linking to other health interventions that can be delivered during immunization contacts. Activities cover: i) immunization systems strengthening, including expansion of immunization services beyond the infant age group; ii) accelerated control of measles and maternal and neonatal tetanus; iii) introduction of new and underutilized vaccines; iv) vaccine supply and immunization financing; and v) disease surveillance and immunization coverage monitoring for tracking global progress.

The Director's Office directs the work of these units through oversight of immunization programme policy, planning, coordination and management. It also mobilizes resources and carries out communication, advocacy and media-related work.

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