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Prevention of varicella and zoster by live attenuated VZV vaccine

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1. ABSTRACT

An effective and safe live attenuated vaccine against varicella zoster virus was developed in Japan in the 1970s and has been in widespread use since the mid-1990s. In the United States, universal vaccination has brought about striking reductions in varicella incidence together with associated hospitalizations and mortality. However, it is clear that varicella will continue to occur even in highly immunized populations, owing to the ability of VZV to reactivate as zoster. In addressing this challenge, attention is currently focused on efforts to minimize the proportion of susceptible individuals by administering a second dose of vaccine to children. The potential of the newly licensed zoster vaccine to reduce viral circulation still further has yet to be evaluated.

2. INTRODUCTION

Like other human herpesviruses, varicella zoster virus (VZV) is a supremely successful pathogen that has co-evolved with us and rarely causes life-threatening disease. In unvaccinated Western populations, VZV is almost universally acquired within the first decade of life, causing the primary disease, chickenpox (varicella). This brief though highly contagious illness allows the virus to establish latent infection of sensory neurons. Epidemiologically, this is the virus's masterstroke since the reactivation of infection as zoster (shingles) in later life affords it a fresh opportunity to spread to new hosts. This feature also lends particular complexity to the implementation of a successful vaccine program against

VZV. Nonetheless, experience in the US is that some 12 years after the introduction of universal varicella vaccination, chickenpox has become an uncommon disease. In contrast, demographic changes in the West mean that herpes zoster is increasingly common in our ageing population, and this effect may be only partially offset by the newly available zoster vaccine.

In the following review, I will briefly outline pertinent features of VZV's epidemiology, clinical features and biology, before describing the development of VZV vaccine and its application to the prevention of varicella and zoster.

3. EPIDEMIOLOGY IN UNVACCINATED POPULATIONS

Varicella results from primary infection with VZV and typically occurs during childhood in temperate climates(1, 2). In the tropics, virus circulation is less and adult infection is more common. The virus is easily acquired by household or face-to-face contact with another case of chickenpox, and somewhat less readily from individuals with the rash of reactivated VZV, shingles. Household attack rates are in excess of 70% and secondary cases tend to be more severe (with more vesicles and greater systemic upset)(3). Disease is endemic but with a seasonal peak in spring. The vast majority of individuals gain lifelong immunity to varicella after their primary infection, although second episodes of varicella have been documented.

In contrast to varicella, herpes zoster shows no seasonality and is generally a disease of older persons, with an age-specific incidence that rises steeply after the sixth decade(4, 5). However, the risk of zoster is also greatly increased in individuals with suppressed cellular immunity at any age, for example those on post-transplant immunosuppressive therapy(6) or with HIV infection(7). In the latter group there have been suggestions that zoster can represent a form of immune reconstitution disease(8, 9), although the strong association between HIV and zoster predates the development of highly active anti-retroviral therapy(10, 11).

Circumstantial evidence links contact with children (a surrogate for VZV exposure) to relative protection against herpes zoster(12, 13). Since amplification of cellular and humoral immune responses can be demonstrated following VZV exposure(14-16), it is certainly plausible that exogenous boosting contributes to anti-viral immunity; indeed, this provides the rationale for zoster vaccination.

4. THE VIRUS

VZV is an alpha-herpesvirus, closely related to Herpes simplex virus (HSV) and yet with many important differences from it. VZV's double-stranded DNA genome comprises some 125 kilobase pairs and 71 open reading frames, all of which appear to be transcribed during productive infection(17). By analogy with HSV, it is frequently stated that VZV genes are expressed in an orderly sequence (immediate early, early and late) during the course of infection. However it has not yet been possible to study this satisfactorily, owing to the current impossibility of obtaining synchronous VZV infection *in vitro*.

What is clear is that VZV produces a highly cytotoxic infection of many human cell types *in vitro*. Viral DNA is synthesized to high copy number within the nucleus, where it is packaged with viral nucleoproteins into nucleocapsids. These exit the nucleus by a process of budding into the perinuclear cisterna, subsequently losing this primary envelope by fusion with the endoplasmic reticulum(18). The resulting naked cytoplasmic nucleocapsids can convey infection to neighbouring cells directly in a fusion process that requires the presence of viral glycoproteins in the plasma membrane(19, 20). This cell-to-cell spread is believed to be the major route of viral propagation within infected hosts as well as *in vitro*, where it leads to the formation of striking syncytia.

A notable feature of VZV, and one which makes Professor Takahashi's achievement in developing a varicella vaccine all the more remarkable, is the fact that so little infectious virus is released into the extracellular space. Tissue supernatant is barely infectious at all, despite being rich in enveloped virus particles(21, 22). By electron microscopy, secondary envelopment has been visualized as occurring at the trans-Golgi network (TGN), where viral glycoproteins appear to recruit tegument-coated nucleocapsids to their cytoplasmic domains(23). Topologically, the viral envelope is acquired by budding into the TGN, resulting in the formation of an enveloped virion within a TGN-derived vesicle. The latter contains cellular transmembrane proteins, notably the cation-independent mannose 6-phosphate receptor (MPR^{ci}), that direct its cargo to the acidic late endosomal compartment of most cell types, resulting in inactivation prior to exocytotic release of virus(23). What makes this explanation all the more compelling is the demonstration that loss of MPR^{ci} expression, either naturally in maturing keratinocytes or artificially by gene silencing technology, allows exiting virions to escape inactivation in the late endosome(24). Thus is explained the paradox of a virus that is extremely cell-associated *in vitro*, yet occurs as highly infectious virions within vesicular fluid *in vivo*.

These skin-derived infectious virions are believed to be responsible for the majority of person-to-person spread of varicella(25), although the possibility of respiratory droplet spread has been inferred from the fact that contagion precedes the development of rash. Recent studies focusing on how virions establish infection have demonstrated that viral entry is an active, endocytic process that requires host cell cholesterol (26) as well as both the MPR^{ci} (a transmembrane receptor)(24) and insulin degrading enzyme (IDE, a soluble protein found in association with cellular membranes)(27). The latter protein also appears to play a role in the cell-associated spread of virus, along with viral glycoproteins(27).

5. PATHOGENESIS

5.1. Varicella

Early events in the pathogenesis of varicella have been extremely difficult to study, owing to the lack of a small animal model of disease. The initial site of infection is assumed to be the respiratory tract(28). During the subsequent incubation period of 10-21 days, VZV is thought to undergo replication in local lymphoid tissue followed by cell-associated viraemic dissemination to the skin and other organs. Infected mononuclear cells have been shown to circulate prior to and during varicella(29, 30), and both lymphocytes and dendritic cells can support virus infection *in vitro*(31, 32). Recently, Arvin and colleagues have suggested that dissemination likely occurs relatively early during the incubation period, based on their observations of the time taken to generate skin lesions in a humanized mouse model of varicella(33). If, as they also postulate, T cells transmit infection only as intact virions(32, 34), this could coincide with the time window for effective post-exposure prophylaxis by passive immunisation (VZIG).

Widespread replication of VZV in the skin produces the intensely pruritic lesions that give chickenpox its name. Skin lesions are most numerous over the trunk, less so on the face and scalp and least on hands and feet; mucous membranes may also be involved(35). Typically, lesions appear in successive crops over 3-7 days, with the result that pox of different ages are seen at any one time. Each lesion evolves through macular and papular phases, often going on to form a vesicle that later becomes pustular. The total number of skin lesions varies greatly from one individual to another, with a median of some 300 in a typical case of varicella(3). Drying and crusting over of skin lesions marks the end of the contagious period, which is usually dated from 24-48 hours prior to the recognition of rash. The rash may also be preceded by prodromal fever, headache and malaise of 1 or more days, particularly in older individuals. Such systemic symptoms typically persist as long as new skin lesions continue to appear; in general, the greater the number of spots, the higher the fever.

In the majority of individuals, chickenpox resolves without specific treatment and does not produce scarring of the skin. The rate of severe or complicated chickenpox is low among immunocompetent children, but nonetheless numbers of such cases are significant because the disease is so common in this age-group(2). The most common complication in the young is secondary bacterial infection of the skin; invasive bacterial disease is also seen, notably group A streptococcal infection. Other complications of chickenpox, such as varicella pneumonia and encephalitis, reflect overwhelming viral infection, and are more likely to occur in the context of defective cell-mediated immunity, (in contrast, those with defective humoral immunity are not at increased risk). Chickenpox is also much more likely to be severe in adults than children, and represents a particular threat to pregnant women as well as their unborn offspring. The reason for this heightened susceptibility is unclear.

5.2. Zoster

The pathogenesis of zoster is currently incompletely understood, as is VZV latency. Classic cutaneous zoster is heralded by pain, dysesthesia and pruritus in a dermatomal distribution, sometimes associated with systemic upset(36). The vesicles that subsequently develop contain infectious virions just as in the case of chickenpox and again contagion ends when all skin lesions crust over. The two major complications of zoster in the immunocompetent are corneal scarring associated with ophthalmic zoster, and post-herpetic neuralgia (PHN). The latter syndrome of persistent dermatomal pain and dysesthesia is particularly common in elderly individuals, and produces a large burden of morbidity(37). Zoster in the immuno-compromised is associated with acute complications that reflect the failure to confine viral replication, namely disseminated cutaneous disease and visceral zoster, as well as a heightened risk of PHN(6, 38).

That the dermatomal distribution of zoster results from viral reactivation in sensory neurons of one dorsal root (or cranial nerve) ganglion was deduced from careful clinical observation by Hope-Simpson(39). Studies of *post mortem* specimens of human neural tissue have confirmed the presence of VZV DNA and have shown that latency is an active state, which sees the transcription and translation of a handful of VZV genes from a postulated episomal viral genome(40-42). Unsurprisingly, there is intense interest in the function of these latency proteins, several of which show a strikingly cytoplasmic distribution during latency that contrasts with nuclear localization during lytic infection. This pattern contrasts with other neurotropic herpesviruses such as HSV, latency of which is silent at protein level (reviewed in (43)). On the other hand, enforced expression of the HSV protein ICP0 can reactivate either virus from latently infected cells *in vitro*. Major goals of current research in this field are to understand how latent infection is established by VZV and how reactivation is triggered within neurons(44).

6. VACCINE DEVELOPMENT - VARICELLA

All varicella vaccines in current use, together with the vaccine recently licensed for zoster prevention in the elderly, contain live virus derived from one attenuated strain of VZV. Attenuation was achieved by Takahashi and colleagues in the 1970s by sequential passage of a clinical isolate of VZV through human and guinea pig cells in tissue culture (45). The resulting virus shows mildly altered behaviour in tissue culture but a striking reduction in pathogenicity *in vivo*(25, 46). This attenuation is attributed to numerous mutations within the vaccine virus, many of which affect the key transcriptional regulator ORF 62(47, 48). However, it has been difficult to achieve a precise understanding of the molecular basis of attenuation, partly because the vaccine contains a mixture of related strains of virus(49) and partly due to the technical difficulty of manipulating the VZV genome *in vitro*.

Early studies of vaccine safety and efficacy were conducted in children being treated for leukemia because

they constituted a major risk group for severe (and fatal) varicella(50, 51). Despite their heightened susceptibility to herpesviral disease, adverse reactions to the vaccine were unusual with the exception of skin rash (40%). Vaccine-related rash could be local or generalized and was transmissible, though much less so than wild type varicella. The efficacy of the vaccine in protecting against varicella was impressive, at over 80% for all varicella and 100% against severe disease(52). Rates of zoster were also significantly reduced among vaccinees, compared with children infected with wild type VZV(53).

Several pre-licensure studies confirmed the efficacy and safety of varicella vaccine in healthy adults and children, albeit with a variety of vaccine potencies and schedules. The vaccine appeared very immunogenic, as measured by serologic assays such as ELISA or FAMA (fluorescent antibody to membrane antigen), but these responses are an imperfect predictor of protection. For example, one large placebo-controlled trial showed 99% seroconversion among children receiving a single dose of vaccine, yet only 72% efficacy in preventing varicella(54). Interestingly, this trial compared two potencies of vaccine, and showed superior efficacy of the higher potency (~10^4 PFU, 88% efficacy) compared with the lower potency vaccine (~10^3 PFU, 55% efficacy). The vaccines subsequently mass-produced for distribution within the US and Europe (*Varivax* (Merck) and *Varilrix* (GSK)) are closer to the lower potency, and were considered highly immunogenic based on the demonstration of antibodies to VZV glycoproteins by ELISA (gpELISA). The best predictor of protection from varicella, however, is the presence of antibodies that can bind detectably to fresh infected cells in a "wet" FAMA(55, 56). A recent study of vaccine immunogenicity "in the field", utilizing this wet FAMA, has suggested that primary vaccine failure may be substantially more common than previously thought (57, 58). The recently licensed, combined measles-mumps-rubella-varicella vaccines contain higher titers of VZV that are required to achieve comparable rates of seroconversion, while zoster vaccine (*Zostavax* (Merck)) is higher still in potency.

7. THE US EXPERIENCE OF VARICELLA VACCINATION

7.1. Recommendations & implementation

In 1996, the ACIP recommended universal vaccination against varicella of susceptible children aged 12-18 months and of other varicella-naïve individuals excepting the immuno-compromised and pregnant women(59). A single dose of vaccine was recommended for infants and children but two doses a month apart from adolescence onwards. Subsequent implementation of the program was relatively rapid, owing to the steady introduction of state requirements for vaccination or a history of varicella for school entry. Uptake of the vaccine in children aged 19-35 months now approaches 90%(60).

In June 2006 the ACIP revised its recommendations to include a second, booster dose of varicella vaccine. For those initially immunized at 12-18 months, this should be given at 4-6 years of age(61). This recommendation was based on the changing epidemiology of breakthrough varicella as will be discussed below. It is too early to comment on the effectiveness of this intervention.

7.2. Effects of universal vaccination on varicella

The impact of varicella vaccination on the epidemiology of VZV has been profound, as documented in a variety of studies. In sentinel regions of the US, studied prospectively by the CDC, varicella incidence declined by 71-84% over the period 1994 to 2000, as vaccination coverage rose to 74-84%(62, 63). Several states in which varicella is notifiable showed a comparable decline in varicella incidence(64). Interestingly, this effect has been experienced among both vaccinated and unvaccinated individuals, including older individuals who are not the focus of the immunization program.

In keeping with this fall in the overall incidence of disease, other studies suggest that the anticipated reductions in morbidity and mortality are being achieved. Thus statistics from large healthcare provider databases show a marked decline in rates of varicella-related consultations and hospitalizations(65). The rate of varicella-related deaths has also plummeted since universal varicella vaccination was implemented(66). Economic evaluation suggests that these benefits have been achieved in a highly cost-effective manner.

Notwithstanding these manifest successes of the universal vaccination program, outbreaks of varicella have continued to occur in the US(67). Some of these have affected highly vaccinated school populations, emphasizing that the vaccine provides incomplete protection against varicella(68-70). Indeed, there is evidence that the vaccine as currently used in the US may be considerably less immunogenic than was suggested by pre-licensure trials(57, 58). Longitudinal study of sentinel populations has suggested that vaccine-induced immunity also wanes markedly over time(62), although the same effect has not been noted in other settings(71). Correspondingly, the vaccine's effectiveness in preventing varicella has ranged from as little as 44% to more than 88% in outbreak settings, while case control studies have indicated effectiveness of around 80% against all varicella, higher against severe disease(summarized in (61)). The continued occurrence of severe and fatal varicella among the unvaccinated has served as a reminder of the potential threat to public health, should the vaccination program falter(72-74). Given that a 2-dose vaccination schedule confers improved immunogenicity and protection against breakthrough disease in children(75), it has been a logical step to introduce a second dose of vaccine in order to reduce viral circulation still further(61). Whether this will be sufficient to stifle a virus that latently infects more than 90% of the population remains to be seen.

7.3. Effects of universal varicella vaccination on zoster

The contributions of viral, host and environmental factors to protection against zoster are not well understood. Vaccine strain virus certainly can

establish latency and can reactivate to cause classical dermatomal zoster that is clinically similar to wild type disease (as confirmed by typing of clinical specimens by polymerase chain reaction(76)). However, early studies in children with leukemia suggested that, at least in this moderately immunocompromised group, vaccine strain VZV was significantly less likely to reactivate than wild type virus(53). Results from a long-term follow-up study in healthy immunized adults showed no excess of zoster among vaccinees(77). While data on healthy children are still emerging, it appears likely that vaccinated individuals will manifest an inherently reduced rate of zoster compared with those who have suffered chickenpox. However, at population level, the latter group will remain more numerous for many decades after the introduction of universal vaccination. If exogenous VZV exposure were to be important for the maintenance of cellular immunity, then rates of zoster would be expected to rise as VZV circulation falls(78, 79). This consideration has been a major barrier to the introduction of universal varicella vaccination outside the US. Experience so far does not suggest a rising tide of zoster in the USA but this possibility is being actively monitored(61, 80, 81). Interpretation is made more difficult by the fact that zoster incidence was increasing well before the introduction of varicella vaccine (4).

8. VACCINE DEVELOPMENT – ZOSTER

In this context of concern over possible adverse effects of varicella vaccination, the development of a safe and efficacious vaccine against zoster was an important goal(82). VZV-specific antibody titers are not predictive of protection against zoster; instead, cellular immunity must be assessed(83). By this measure, a high potency vaccine was safe and immunogenic in older sero-positive adults (84). A meticulously executed study by Oxman *et al* in over 38000 elderly adults subsequently showed this vaccine to confer 50% protection against all zoster and a 67% reduction in PHN over a median of 3 years' follow-up(85). Despite its expense, this vaccine is expected to be highly cost-effective because zoster is so expensive to treat(37). The vaccine has therefore been licensed in the US, although questions remain as to the duration of protection and possible need for further doses. Provisional recommendations from the ACIP in 2006 suggest the administration of a single dose of zoster vaccine to individuals over the age of 60, irrespective of any history of herpes zoster(86). The safety and efficacy of live zoster vaccine in the immunocompromised has yet to be addressed. An experimental killed VZV vaccine was helpful against zoster in patients undergoing autologous HSCT in a small study(87).

9. VZV VACCINATION OUTSIDE THE US

VZV is overshadowed in importance as a pathogen in the developing world by numerous potentially preventable infectious diseases. Furthermore, the varicella vaccine is expensive and heat-labile, two considerations that substantially reduce its utility in that setting. Current efforts are directed towards more pressing vaccine-preventable diseases in resource-poor countries. Conversely, a number of developed nations have begun implementation of US-style programs of universal varicella vaccination or have plans to do so(88, 89). Analyses of cost effectiveness have been important drivers for such policies.

Other countries, for example the UK, remain to be convinced of the longterm sustainability of universal varicella vaccination. Mathematical models of the public health impact of such programs are sensitive to several variables: high rates of primary vaccine failure, loss of immunity over time or failure to achieve sufficient (>90%) coverage could all jeopardize success(79, 90). The worst case scenario would see growing numbers of susceptible adults in whom high rates of severe and fatal varicella could be anticipated during epidemics. A further concern is the possibility of a significant increase in zoster over time, as discussed above. These considerations currently militate against the implementation of universal varicella vaccination in many European countries(88). A variety of alternative strategies include the targeted vaccination of varicella-susceptible adolescents and adults, healthcare workers and household contacts of the immunocompromised. There is also increasing interest in the possibility of extending vaccination to selected immunocompromised susceptibles, including HIV-infected children and candidates for solid organ transplantation. Such programs do not address the major burden of varicella-related morbidity and mortality, which is borne by healthy children; nor the associated economic cost of parental absence from work. This debate is therefore set to continue well into the twenty-first century.

10. CONCLUSIONS

The live attenuated vaccine has shown itself to be an extremely powerful tool in reducing varicella-related morbidity and mortality, yet anxieties remain as to the safest strategy for its use. The world looks to the USA as its story of varicella vaccination continues to unfold. The availability of MMRV vaccines is expected to simplify the implementation of two-dose varicella immunization schedules. Administration of a higher potency VZV vaccine to older adults is a promising strategy for the prevention of zoster.

11. REFERENCES

1. Wharton M.: The epidemiology of varicella-zoster virus infections. Infect Dis Clin N Amer, 10, 571-581 (1996)

2. Seward J. F., K. Galil and M. Wharton: Epidemiology of varicella. In: Varicella-Zoster Virus: Virology and Clinical Management. Eds Arvin A&A Gershon, Cambridge University Press, Cambridge (2000)

3. Ross A. H., E. Lencher and G. Reitman: Modification of chickenpox in family contacts by administration of gamma globulin. N Engl J Med, 267, 369-376 (1962)

4. Donahue J. G., P. W. Choo, J. E. Manson and R. Platt: The incidence of herpes zoster. Arch Intern Med, 155(15), 1605-1609 (1995)

5. Insinga R. P., R. F. Itzler, J. M. Pellissier, P. Saddier and A. A. Nikas: The incidence of herpes zoster in a United States administrative database. J Gen Intern Med, 20(8), 748-753 (2005)

6. Gourishankar S., J. C. McDermid, G. S. Jhangri and J. K. Preiksaitis: Herpes zoster infection following solid organ transplantation: incidence, risk factors and outcomes in the current immunosuppressive era. Am J Transplant, 4(1), 108-115 (2004)

7. Seidlein von L., S. G. Gillette, Y. Bryson, T. frederick, L. Mascola, J. Church, P. Brunell, A. Kovaks, A. Deveikis and M. Keller: Frequent recurrence and persistence of varicella-zoster virus infections in children infected with human immunodeficiency virus type 1. J Pediatr, 128, 52-57 (1996)

8. Domingo P., O. H. Torres, J. Ris and G. Vazquez: Herpes zoster as an immune reconstitution disease after initiation of combination antiretroviral therapy in patients with human immunodeficiency virus type-1 infection. Am J Med, 110(8), 605-609 (2001)

9. Tangsinmankong N., W. Kamchaisatian, J. Lujan-Zilbermann, C. L. Brown, J. W. Sleasman and P. J. Emmanuel: Varicella zoster as a manifestation of immune restoration disease in HIV-infected children. J Allergy Clin Immunol, 113(4), 742-746 (2004)

10. Colebunders R., J. Mann, H. Francis, K. Bila, I. L., M. Ilwaya, N. Kakonde, T. Quinn, C. J. and P. Piot: Herpes zoster in African patients: a clinical predictor of human immunodeficiency virus infection. J Infect Dis, 157, 314-319 (1988)

11. Patterson L., K. Butler and M. Edwards: Clinical herpes zoster shortly following primary varicella in two HIV-infected children. Clin Pediatr, 28, 354 (1989)

12. Thomas S., J. Wheeler and A. J. Hall: Contacts with varicella or with children and protection against herpes zoster in adults: a case-control study. Lancet, 360(Aug 31), 678-682 (2002)

13. Brisson M., N. J. Gay, W. J. Edmunds and N. J. Andrews: Exposure to varicella boosts immunity to herpes-zoster: implications for mass vaccination against chickenpox. Vaccine, 20, 2500-2507 (2002)

14. Arvin A. M.: Immune responses to varicella-zoster virus. Infect Dis Clin North Am, 10, 529-570 (1996)

15. Vossen M. T., M. R. Gent, J. F. Weel, M. D. de Jong, R. A. van Lier and T. W. Kuijpers: Development of virus-specific CD4+ T cells on reexposure to Varicella-Zoster virus. J Infect Dis, 190(1), 72-82 (2004)

16. Gershon A., P. LaRussa, S. Steinberg, S. H. Lo, N. Mervish and P. Meier: The protective effect of immunologic boosting against zoster: an analysis in leukemic children who were vaccinated against chickenpox. J Infect Dis, 173, 450-453 (1996)

17. Cohrs R. J., M. P. Hurley and D. H. Gilden: Array analysis of viral gene transcription during lytic infection of cells in tissue culture with Varicella-Zoster virus. J Virol, 77(21), 11718-11732 (2003)

18. Zhu Z., M. D. Gershon, R. Ambron, C. Gabel and A. A. Gershon: Infection of cells by varicella zoster virus: inhibition of viral entry by mannose 6-phosphate and heparin. Proc Natl Acad Sci U S A, 92(8), 3546-3550 (1995)

19. Duus K. M., C. Hatfield and C. Grose: Cell surface expression and fusion by the varicella-zoster virus gH:gL glycoprotein complex. Analysis by laser scanning microscopy. Virology, 210, 429-440 (1995)

20. Maresova L., T. J. Pasieka and C. Grose: Varicella-zoster virus gB and gE coexpression, but not gB or gE alone, leads to abundant fusion and syncytium formation equivalent to those from gH and gL coexpression. J Virol, 75(19), 9483-9492. (2001)

21. Cook M. L. and J. Stevens: Labile coat: reason for noninfectious cell-free varicella zoster virus in culture. J Virol, 2, 1458-1464 (1968)

22. Cook M. L. and J. G. Stevens: Replication of varicella-zoster virus in cell cultures. An ultrastructural study. J Ultrastruct Res, 32, 334-350 (1970)

23. Gershon A. A., D. L. Sherman, Z. Zhu, C. A. Gabel, R. T. Ambron and M. D. Gershon: Intracellular transport of newly synthesized varicella-zoster virus: final envelopment in the trans-Golgi network. J Virol, 68(10), 6372-6390 (1994)

24. Chen J., Z. Zhu, A. Gershon and M. Gershon: Dependence of the entry and cell association of varicella zoster virus on the cation-independent mannose 6-phosphate receptor *in vitro* and in the skin of human patients with varicella and zoster. Cell, 119(6) (2004)

25. Tsolia M., A. Gershon, S. Steinberg and L. Gelb: Live attenuated varicella vaccine: evidence that the virus is attenuated and the importance of skin lesions in transmission of varicella-zoster virus. J Pediatr, 116, 184-189 (1990)

26. Hambleton S., S. P. Steinberg, M. D. Gershon and A. A. Gershon: Cholesterol dependence of varicella-zoster virion entry into target cells. J Virol, 81(14), 7548-7558 (2007)

27. Li Q., M. A. Ali and J. I. Cohen: Insulin degrading enzyme is a cellular receptor mediating varicella-zoster

virus infection and cell-to-cell spread. Cell, 127(2), 305-316 (2006)

28. Grose C., M. Ye and J. A. Padilla: Pathogenesis of primary infection. In: Varicella-zoster virus: Virology and clinical management. Eds Arvin AM & AA Gershon, Cambridge University Press, Cambridge (2000)

29. Asano Y., N. Itakura, Y. Kajita, S. Suga, T. Yoshikawa, T. Yazaki, T. Ozaki, Y. Yamanishi and M. Takahashi: Severity of viremia and clinical findings in children with varicella. J Infect Dis, 161, 1095-1098 (1990)

30. Mainka C., B. Fuss, H. Geiger, H. Hofelmayr and M. H. Wolff: Characterization of viremia at different stages of varicella-zoster virus infection. J Med Virol, 56, 91-98 (1998)

31. Abendroth A., G. Morrow, A. L. Cunningham and B. Slobedman: Varicella-zoster virus infection of human dendritic cells and transmission to T cells: implications for virus dissemination in the host. J Virol, 75(13), 6183-6192. (2001)

32. Moffat J. F., M. D. Stein, H. Kaneshima and A. M. Arvin: Tropism of varicella-zoster virus for human CD4+ and CD8+ T lymphocytes and epidermal cells in SCID-hu mice. J Virol, 69, 5236-5242 (1995)

33. Ku C. C., L. Zerboni, H. Ito, B. S. Graham, M. Wallace and A. M. Arvin: Varicella-zoster virus transfer to skin by T Cells and modulation of viral replication by epidermal cell interferon-alpha. J Exp Med, 200(7), 917-925 (2004)

34. Besser J., M. Ikoma, K. Fabel, M. H. Sommer, L. Zerboni, C. Grose and A. M. Arvin: Differential requirement for cell fusion and virion formation in the pathogenesis of varicella-zoster virus infection in skin and T cells. J Virol, 78(23), 13293-13305 (2004)

35. LaRussa P.: Clinical manifestations of varicella. In: Varicella-zoster virus: virology and clinical management. Eds Arvin AM & AA Gershon, Cambridge University Press, Cambridge (2000)

36. Oxman M. N.: Clinical manifestations of herpes zoster. In: Varicella-Zoster Virus: Virology and Clinical Management. Eds Arvin AM & AA Gershon, Cambridge University Press, Cambridge (2000)

37. Edmunds W. J., M. Brisson and J. D. Rose: The epidemiology of herpes zoster and potential cost-effectiveness of vaccination in England and Wales. Vaccine, 19(23-24), 3076-3090 (2001)

38. Gershon A. A.: Zoster in Immunosuppressed Patients. In: Herpes Zoster and Postherpetic Neuralgia. Eds Watson CPN & AA Gershon, Elsevier, Amsterdam (2001)

39. Hope-Simpson R. E.: The nature of herpes zoster: a long term study and a new hypothesis. Proc Roy Soc Med, 58, 9-20 (1965)

40. Lungu O., P. Annunziato, A. Gershon, S. Stegatis, D. Josefson, P. LaRussa and S. Silverstein: Reactivated and latent varicella-zoster virus in human dorsal root ganglia. Proc Nat Acad Sci USA, 92, 10980-10984 (1995)

41. Cohrs R. J., D. H. Gilden, P. R. Kinchington, E. Grinfeld and P. G. Kennedy: Varicella-Zoster Virus Gene 66 Transcription and Translation in Latently Infected Human Ganglia. J Virol, 77(12), 6660-6665 (2003)

42. Grinfeld E. and P. Kennedy: Translation of varicella-zoster virus genes during human ganglionic latency. Virus Genes, 29(3), 317-319 (2004)

43. Mitchell B. M., D. C. Bloom, R. J. Cohrs, D. H. Gilden and P. G. Kennedy: Herpes simplex virus-1 and varicella-zoster virus latency in ganglia. J Neurovirol, 9(2), 194-204 (2003)

44. Kennedy P. G.: Varicella-zoster virus latency in human ganglia. Rev Med Virol, 12(5), 327-334 (2002)

45. Gershon A. A., M. Takahashi and J. Seward: Varicella Vaccine. In: Vaccines. Eds Plotkin S&W Orenstein, WB Saunders, Philadelphia, PA (2004)

46. Moffat J. F., L. Zerboni, P. Kinchington, C. Grose, H. Kaneshima and A. Arvin: Attenuation of the vaccine Oka strain of varicella-zoster virus and role of glycoprotein C in alphaherpesvirus virulence demonstrated in the SCID-hu mouse. J Virol, 72, 965-974 (1998)

47. Gomi Y., T. Imagawa, M. Takahashi and K. Yamanishi: Oka varicella vaccine is distinguishable from its parental virus in DNA sequence of open reading frame 62 and its transactivation activity. J Med Virol, 61, 497-503 (2000)

48. Gomi Y., T. Imagawa, M. Takahashi and K. Yamanishi: Comparison of DNA sequence and transactivation activity of open reading frame 62 of Oka varicella vaccine and its parental viruses. Arch Virol, S17, 49-56 (2001)

49. Quinlivan M. L., A. A. Gershon, S. P. Steinberg and J. Breuer: Rashes occurring after immunization with a mixture of viruses in the Oka vaccine are derived from single clones of virus. J Infect Dis, 190(4), 793-796 (2004)

50. Feldman S., W. Hughes and C. Daniel: Varicella in children with cancer: 77 cases. Pediatrics, 80, 388-397 (1975)

51. Gershon A., P. LaRussa and S. Steinberg: Varicella vaccine: clinical trials in immunocompromised patients. Infect Dis Clin North Am, 10(3), 583-594 (1996)

52. Gershon A. A., S. Steinberg, L. Gelb and NIAID-Collaborative-Varicella-Vaccine-Study-Group.: Live attenuated varicella vaccine: efficacy for children with leukemia in remission. JAMA, 252, 355-362 (1984)

53. Hardy I. B., A. Gershon, S. Steinberg and P. LaRussa: The incidence of zoster after immunization with live attenuated varicella vaccine. A study in children with leukemia. N Engl J Med, 325, 1545-1550 (1991)

54. Vesikari T. and e. al: Efficacy of high titer live attenuated varicella vaccine in healthy young children. J Infect Dis, 174S, S330-334 (1996)

55. Gershon A.: Varicella-zoster virus: prospects for control. Adv Ped Infect Dis, 10, 93-124 (1995)

56. Williams V., A. Gershon and P. Brunell: Serologic response to varicella-zoster membrane antigens measured by indirect immunofluorescence. J Infect Dis, 130, 669-672 (1974)

57. Michalik D. E., P. S. LaRussa, S. P. Steinberg, P. F. Wright, K. M. Edwards and A. A. Gershon: Primary Immune Failure after One Dose of Varicella Vaccine are Likely a Cause of Breakthrough Infections in Healthy Vaccinated Children. Abstract 146, I.D.S.A. Conference, Toronto (2006)

58. Michalik D. E., S. P. Steinberg, P. S. LaRussa, K. M. Edwards, P. F. Wright, A. M. Arvin, H. A. Gans and A. A. Gershon: Primary Vaccine Failure After One Dose of Varicella Vaccine in Healthy Children. Journal of Infectious Diseases (In press)

59. Centers for Disease Control: Prevention of varicella: Recommendations of the Advisory Committee on Immunization Practices (ACIP). Morb Mort Week Rep, 45, 1-36 (1996)

60. Centers-for-Disease-Control: National, state, and urban area vaccination coverage among children aged 19-35 months--United States, 2005. Morb Mortal Wkly Rep, 55(36), 988-993 (2006)

61. Marin M., D. Guris, S. S. Chaves, S. Schmid and J. F. Seward: Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep, 56(RR-4), 1-40 (2007)

62. Chaves S. S., P. Gargiullo, J. X. Zhang, R. Civen, D. Guris, L. Mascola and J. F. Seward: Loss of vaccine-induced immunity to varicella over time. N Engl J Med, 356(11), 1121-1129 (2007)

63. Seward J. F., B. M. Watson, C. L. Peterson, L. Mascola, J. W. Pelosi, J. X. Zhang, T. J. Maupin, G. S. Goldman, L. J. Tabony, K. G. Brodovicz, A. O. Jumaan and M. Wharton: Varicella disease after introduction of varicella vaccine in the United States, 1995-2000. JAMA, 287(5), 606-611 (2002)

64. Centers for Disease Control: Decline in annual incidence of varicella - selected states, 1990-2001. Morb Mort Week Rep, 52, 884-885 (2003)

65. Zhou F., R. Harpaz, A. O. Jumaan, C. A. Winston and A. Shefer: Impact of varicella vaccination on health care utilization. JAMA, 294(7), 797-802 (2005)

66. Nguyen H. Q., A. O. Jumaan and J. F. Seward: Decline in mortality due to varicella after implementation of varicella vaccination in the United States. N Engl J Med, 352, 450-458 (2005)

67. Hambleton S. and A. A. Gershon: The impact of varicella vaccination in the United States. Semin Pediatr Infect Dis, 16(1), 38-43 (2005)

68. Galil K., B. Lee, T. Strine, C. Carraher, A. L. Baughman, M. Eaton, J. Montero and J. Seward: Outbreak of varicella at a day-care center despite vaccination. N Eng J Med, 347(Dec. 12), 1909-1915 (2002)

69. Lee B. R., S. L. Feaver, C. A. Miller, C. W. Hedberg and K. R. Ehresmann: An elementary school outbreak of varicella attributed to vaccine failure: policy implications. J Infect Dis, 190(3), 477-483 (2004)

70. Tugwell B. D., L. E. Lee, H. Gillette, E. M. Lorber, K. Hedberg and P. R. Cieslak: Chickenpox outbreak in a highly vaccinated school population. Pediatrics, 113(3 Pt 1), 455-459 (2004)

71. Vazquez M., P. S. LaRussa, A. A. Gershon, L. M. Niccolai, C. E. Muehlenbein, S. P. Steinberg and E. D. Shapiro: Effectiveness over time of varicella vaccine. JAMA, 291(7), 851-855 (2004)

72. Centers for Disease Control: Varicella-related deaths--United States, 2002. Morb Mortal Wkly Rep, 52(23), 545-547 (2003)

73. McCoy L., F. Sorvillo and P. Simon: Varicella-related mortality in California, 1988-2000. Pediatr Infect Dis J, 23(6), 498-503 (2004)

74. Centers for Disease Control: Varicella-related deaths--United States, January 2003-June 2004. Morb Mortal Wkly Rep, 54(11), 272-274 (2005)

75. Kuter B., H. Matthews, H. Shinefield, S. Black, P. Dennehy, B. Watson, K. Reisinger, L. L. Kim, L. Lupinacci, J. Hartzel and I. Chan: Ten year follow-up of healthy children who received one or two injections of varicella vaccine. Pediatr Infect Dis J, 23(2), 132-137 (2004)

76. LaRussa P., S. Steinberg, E. Shapiro, M. Vazquez and A. Gershon: Viral strain identification in varicella vaccinees with disseminated rashes. Ped Infect Dis J, 19, 1037-1039 (2000)

77. Hambleton S., S. P. Steinberg, P. S. LaRussa, E. D. Shapiro and A. A. Gershon: Risk of herpes zoster in adults immunized with varicella vaccine. Journal of Infectious Diseases (in press)

78. Brisson M. and W. J. Edmunds: The cost-effectiveness of varicella vaccination in Canada. Vaccine, 20(7-8), 1113-1125. (2002)

79. Brisson M., W. J. Edmunds and N. J. Gay: Varicella vaccination: impact of vaccine efficacy on the epidemiology of VZV. J Med Virol, 70 Suppl 1, S31-37 (2003)

80. Jumaan A. O., O. Yu, L. A. Jackson, K. Bohlke, K. Galil and J. F. Seward: Incidence of herpes zoster, before and after varicella-vaccination-associated decreases in the incidence of varicella, 1992-2002. J Infect Dis, 191(12), 2002-2007 (2005)

81. Yih W. K., D. R. Brooks, S. M. Lett, A. O. Jumaan, Z. Zhang, K. M. Clements and J. F. Seward: The incidence of varicella and herpes zoster in Massachusetts as measured by the Behavioral Risk Factor Surveillance System (BRFSS) during a period of increasing varicella vaccine coverage, 1998-2003. BMC Public Health, 5(1), 68 (2005)

82. Levin M. J.: Use of varicella vaccines to prevent herpes zoster in older individuals. Arch Virol Suppl, 17, 151-160 (2001)

83. Burke B. L., R. W. Steele, O. W. Beard, J. S. Wood, T. D. Cain and D. J. Marmer: Immune responses to varicella-zoster in the aged. Arch Intern Med, 142, 291-293 (1982)

84. Levin M. J., J. G. Smith, R. M. Kaufhold, D. Barber, A. R. Hayward, C. Y. Chan, I. S. Chan, D. J. Li, W. Wang, P. M. Keller, A. Shaw, J. L. Silber, K. Schlienger, I. Chalikonda, S. J. Vessey and M. J. Caulfield: Decline in varicella-zoster virus (VZV)-specific cell-mediated immunity with increasing age and boosting with a high-dose VZV vaccine. J Infect Dis, 188(9), 1336-1344 (2003)

85. Oxman M. N., M. J. Levin, G. R. Johnson, K. E. Schmader, S. E. Straus, L. D. Gelb, R. D. Arbeit, M. S. Simberkoff, A. A. Gershon, L. E. Davis, A. Weinberg, K. D. Boardman, H. M. Williams, J. H. Zhang, P. N. Peduzzi, C. E. Beisel, V. A. Morrison, J. C. Guatelli, P. A. Brooks, C. A. Kauffman, C. T. Pachucki, K. M. Neuzil, R. F. Betts, P. F. Wright, M. R. Griffin, P. Brunell, N. E. Soto, A. R. Marques, S. K. Keay, R. P. Goodman, D. J. Cotton, J. W. Gnann, Jr., J. Loutit, M. Holodniy, W. A. Keitel, G. E. Crawford, S. S. Yeh, Z. Lobo, J. F. Toney, R. N. Greenberg, P. M. Keller, R. Harbecke, A. R. Hayward, M. R. Irwin, T. C. Kyriakides, C. Y. Chan, I. S. Chan, W. W. Wang, P. W. Annunziato and J. L. Silber: A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med, 352(22), 2271-2284 (2005)

86. ACIP: Provisional Recommendations for the Use of Zoster Vaccine. (2006) At: http://www.cdc.gov/vaccines/recs/provisional/downloads/zoster-11-20-06.pdf , accessed 09.25.07.

87. Hata A., H. Asanuma, M. Rinki, M. Sharp, R. M. Wong, K. Blume and A. M. Arvin: Use of an inactivated varicella vaccine in recipients of hematopoietic- cell transplants. N Engl J Med, 347(1), 26-34. (2002)

88. Sengupta N., R. Booy, H. J. Schmitt, H. Peltola, P. Van-Damme, R. F. Schumacher, M. Campins, C. Rodrigo, T. Heikkinen, J. Seward, A. Jumaan, A. Finn, P. Olcen, N. Thiry, C. Weil-Olivier and J. Breuer: Varicella vaccination in Europe: are we ready for a universal childhood programme? Eur J Pediatr (2007)

89. Vesikari T., C. Sadzot-Delvaux, B. Rentier and A. Gershon: Increasing Coverage and Efficiency of Measles, Mumps, and Rubella Vaccine and Introducing Universal Varicella Vaccination in Europe: A Role for the Combined Vaccine. Pediatr Infect Dis J, 26(7), 632-638 (2007)

90. Halloran M. E.: Epidemiologic effects of varicella vaccination. Infect Dis Clin N Amer, 10, 631-656 (1996)

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