Published in final edited form as:

J Infect. 2017 June ; 74(Suppl 1): S27–S33. doi:10.1016/S0163-4453(17)30188-3.

Is chickenpox so bad, what do we know about immunity to varicella zoster virus, and what does it tell us about the future?

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Summary

Varicella and zoster continue to cause significant morbidity and even mortality in children and adults. Complications include bacterial superinfection, central nervous system manifestations such as meningitis, encephalitis, and cerebellar ataxia, and pain syndromes especially post herpetic neuralgia. Many developed countries but not all, are now administering live attenuated varicella vaccine routinely, with a decrease in the incidence of disease, providing personal and herd immunity. There is some controversy, however, in some countries concerning whether a decrease in the circulation of wild type virus will result in loss of immunity to VZV in persons who have already had varicella. This manuscript reviews the complications of varicella and zoster in detail, the reasons for development of vaccines against these diseases, complications of vaccinations, and mechanisms by which immunity to this virus develops and is maintained. There are strong indications that the best way to control disease and spread of this virus is by vaccination against both.

Keywords

Varicella; Chickenpox; Zoster; Vaccination; Latency; Reactivation

Introduction

On August 2, 2016, a policy piece entitled “Worst case of chickenpox sparks call for rethink on vaccination” appeared in the Guardian newspaper; this was only about 2 weeks following the summer Oxford Infection & Immunity in Children course of 2016. A toddler whose mother had great difficulty locating a physician who took her child’s illness seriously, was hospitalized for 5 days with severe varicella and received treatment with “antiviral drugs, antibiotics, and morphine”. Fortunately the child survived, but his mother wondered why vaccination against varicella was not being performed in Britain in comparison with many other countries. In this article reference was also made to an earlier publication in the Guardian by Jenny Rohn, on May 15, 2014, entitled “What’s the real reason Britons are not

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Conflict of Interest

Prof Anne Gershon consults for GSK and has service contracts with Merck, both in relation to VZV.

offered the chickenpox vaccine?” Reference is made as to how horrendous varicella disease can be, that skin scarring can occur, and that a major complication is infection with “flesh eating” streptococci. After much discussion, this article concluded that the real reason that varicella vaccine is not recommended by the National Health Service is fear that herd immunity generated by children with varicella might result in an increase in herpes zoster in adults. The author stated that “sick children should not be exploited as living vaccines for older people when there is a perfectly serviceable jab on the market – especially as the evidence that they really do stimulate a protective response against older people’s shingles is not very robust.” Because in the eyes of some, the issue of routine use of varicella vaccine appears to be controversial, this manuscript will present how and why infection with varicella zoster virus (VZV) is not necessarily benign, with elaboration of how immunity to VZV develops and is maintained, and how vaccination can be useful.

Complications of varicella and zoster

Varicella is a highly contagious disease that not only causes an acute infection but also results in lifetime latency of VZV. The body is unable to eliminate this neurotropic virus after illness, and it therefore may subsequently reactivate and cause further diseases. The following are the most common complications of varicella itself: bacterial superinfection of skin, encephalitis, cerebellar ataxia, pneumonia (from VZV or bacteria), and other medical problems that are unusual or rare. Superinfections with Group A streptococci may be particularly severe and even fatal.¹ Latent VZV is confined to ganglionic neurons, from which it is probably prevented from reactivating at least in part by the immune system. In an estimated 30% of individuals, symptomatic reactivation, herpes zoster, occurs over a lifetime, and when zoster develops in the elderly, a serious pain syndrome, post-herpetic neuralgia (PHN) may result in roughly 15% of individuals. Zoster is usually (but not always) manifested by a painful and/or pruritic unilateral dermatomal rash. Other complications of zoster include meningoencephalitis, myelitis, cranial nerve palsies, vasculopathy, gastrointestinal disease, and stroke.² Because both varicella and zoster go hand-in-hand, it is not surprising that there is considerable overlap in clinical complications.^{2,3}

When varicella occurs in a pregnant woman, her off spring may develop the congenital varicella syndrome with particular damage to the central nervous system (CNS), or severe acute disseminated varicella, depending on the timing of the maternal chickenpox. Since varicella is more severe in adults than in children, maternal varicella may also be a very serious and even fatal infection in the mother herself. Fortunately, in contrast to varicella which is transmitted from mother to fetus in about 2% of instances, VZV is almost never transmitted to the fetus or newborn when a pregnant woman develops zoster.^{2,3}

Varicella is likely to be severe in patients whose immunity is compromised, either due to a congenital immunodeficiency, transplantation, or various treatments for malignant or autoimmune disease. These patients are particularly prone to develop pneumonia and hepatitis due to VZV, which may be fatal. Both varicella and zoster are contagious, particularly from skin lesions, which harbor the highly infectious virions that can be aerosolized to spread to others who are susceptible to varicella. Individuals who have recovered from varicella only rarely develop second attacks. There is only 1 serotype of

VZV although there are at least 9 clades, which vary according to geographical location. Most viruses in the western hemisphere belong to clades 1 and 3; clade 2 includes many Asian viruses. VZVs may be typed by various molecular methods, which may identify a particular virus as vaccine or wild type; these methods may be particularly useful in sorting out apparent complications of varicella vaccination.^{2,3}

Details of latency of VZV remain incompletely understood, although it is widely accepted that latency occurs exclusively in neurons.²⁻⁴ There are essentially two theories as to how latency is maintained. One is that the normal cascade of VZV gene expression, involving 71 unique genes, is interrupted, resulting in lack of production of complete infectious virions, termed lytic infection. According to this theory, as many as 6 early genes of VZV are expressed, but then viral gene expression is halted, structural or late genes are not produced, and virions are not formed. These data have emerged from the study of autopsy specimens and also from specimens from the enteric nervous system (ENS) obtained at surgery.⁵⁻⁷ Recently, some studies have questioned the degree of gene expression during latency and have likened the process in VZV to that of herpes simplex virus (HSV) in which latency associated transcripts only are produced in latent infection.^{7,8} In contrast, data from *in vitro* model systems of neurons produced from human stem cells in culture have suggested that during latency there is widespread gene expression of all classes of VZV genes in small quantities, including structural ones without proteins and infectious virions are not made.^{9,10} Future research may clarify which of these mechanisms is most likely operative. It appears that the immune system, in particular CD4 and CD8 lymphocytes are at least partially involved in restraining latent VZV so that infectious virions cannot be produced^{11,12} although the exact mechanism is not understood.

One location where VZV can become latent and reactivate without producing rash is in the ENS; patients with unexplained abdominal pain, gastric and duodenal ulcers, and achalasia due to VZV have been reported.¹³ Neurons from the ENS do not project to the skin, which usually prevents rash from occurring. One method to screen for gastrointestinal involvement by VZV is to test saliva for the presence of VZV DNA.¹⁴ As will be discussed subsequently, testing of saliva can also be a means to identify asymptomatic VZV reactivation. VZV reactivation without rash has also been identified in cases of giant cell arteritis and temporal arteritis.¹⁵⁻¹⁹ Again, VZV reactivation in these autonomic neurons does not cause rash because the neurons do not project to skin. However, VZV particles have been observed in the arterial walls of some of these patients. It is unknown if these complications of VZV reactivation are identifiable by testing of saliva for VZV DNA. At least one case of Takayasu arteritis has been successfully treated with aciclovir.¹⁵ This litany of woes caused by VZV is incomplete, but does argue that it is difficult to stand idly by and not try to prevent illnesses caused by this virus using a vaccine that is known to be safe and effective.

Development of live attenuated varicella vaccine

In 1974, Takahashi reported attenuation of VZV in cell culture by traditional methods, which led to development of a vaccine to prevent varicella.²⁰ This scientific discovery was met with a great degree of questioning and criticism, especially with regard to fears surrounding the poor understanding of VZV latency and reactivation, and also the worry that

immunity from vaccination might not be long lasting.^{21–23} By the late 1970s, acute leukemia in children was frequently being cured, but many of these patients suffered severe morbidity and even mortality from varicella.^{24,25} Lifesaving studies of varicella vaccine in Japan and the United States soon showed that the vaccine was safe and effective even in these immunocompromised patients who were judged to have the most to gain and least to lose from vaccination.^{26–28} These studies paved the way for additional clinical vaccine trials in healthy children and adults, which were also highly successful.^{29–31} Today live attenuated varicella vaccine is used extensively, and hundreds of millions of doses have been distributed around the world. Its success in prevention of varicella led directly to the development of a similar but more potent live vaccine to prevent zoster in the elderly. Varicella vaccine was licensed for universal immunization of healthy children in the United States in 1995; zoster vaccine followed in 2006. These are the only licensed vaccines for prevention of infection by a human herpesvirus. Today in the US 90% of healthy children have been immunized against varicella.^{2,3,32,33}

Since the licensure of varicella vaccine, the incidence of varicella disease in the US has fallen by 90%, particularly after the 2 dose schedule was implemented in 2006.^{34,35} A similar decrease in hospitalizations has occurred, as well as a decrease in mortality of over 90%.³⁶ Millions of dollars in health related costs have been saved by the routine use of varicella vaccine. When only 1 dose of vaccine was recommended, outbreaks of varicella continued to plague schools, but with the routine use of 2 doses these outbreaks have almost disappeared.³ Two doses of varicella vaccine prevents disease in 98% of vaccines.³⁷ Waning of immunity against varicella after vaccination has not been observed. As will be further discussed, it is possible that periodic reactivation of VZV in the absence of symptoms contributes to maintenance of immunity.^{4,35,38} It may be that latency of VZV, initially thought to be a possible disadvantage of the vaccine is in reality an advantage that helps to maintain long-term immunity to the virus.

Immunity to VZV

The mechanisms of immunity to this virus are complex and even now not entirely understood. It seems highly likely that specific antibodies play a role in protection against varicella in susceptible individuals who have been exposed to VZV, which is borne out by the reported efficacy of passive immunization in healthy and immunocompromised children exposed to VZV.^{39,40} Moreover, the fluorescent antibody to membrane antigen (FAMA) assay was used successfully as an immune correlate in clinical trials of vaccination of children with underlying leukemia.^{26,41} The FAMA assay measures antibodies to VZV glycoprotein E, which is the major viral glycoprotein. Over many years of study, it was determined that the presence of this antibody in serum is indicative of immunity against varicella although not against zoster. Of 131 seropositive individuals closely exposed to varicella, only 2% developed chickenpox (both cases were mild). In contrast, of 68 individuals who lacked this antibody on household exposure to VZV, 59% developed varicella within the next 3 weeks.⁴² Nevertheless, cellular immunity also must play a role in protection against varicella because children with isolated agammaglobulinemia are not subject to recurrent varicella while, reactivation of VZV and development of zoster occurs despite the presence of serum antibodies to the virus.³

Cellular immunity is thought to be required for recovery from disease and prevention of reactivation from latency. Hope-Simpson was the first to describe the increasing incidence of zoster with increasing age.⁴³ Later it was established that cellular immunity to VZV in blood is progressively lost with aging, and more recently an increase in regulatory T cells (Tregs) was noted in the skin of the elderly and may be associated with development of zoster.^{44–46} When severe zoster emerged as a major problem for immunosuppressed children being treated for cancer, and also in children infected with human immunodeficiency virus (HIV), it was proposed that zoster is related to depletion of T lymphocytes (CD4 and CD8).^{47,48} It was eventually noted that HIV-infected children receiving protease inhibitors had better preservation of T lymphocytes accompanied by a lower risk of developing zoster.⁴⁸

The increasing use of varicella vaccine in children who appeared to be healthy led to further elucidation of cellular immunity against VZV. The importance of T cell (adaptive) immunity in host defense against VZV continued to emerge. In varicella vaccinees, 5 fatalities were ascribed to live attenuated varicella vaccine: a child with leukemia in remission for only 5 months when vaccinated,⁴⁹ an adult with lymphoma who had undergone a stem cell transplant,⁵⁰ and 3 children with unrecognized immunodeficiency disease when vaccinated. These included initially unrecognized forms of severe immunodeficiency disease, RAG 2 deficiency and ADA deficiency.^{51–54} Severe adverse reactions after vaccination but with recovery after antiviral therapy were observed in a child with undiagnosed HIV infection,⁵⁵ DOCK 2 deficiency, DOCK 8 deficiency with hyper-IgE and STAT mutations; some of these children also had functional abnormalities of natural killer (NK) cells.^{56–60} Rarely, children with severe varicella who only lacked natural killer cells (NK) have been described, further implicating innate immunity in host defense against VZV.^{61,62} NK lymphocytes, which function along with Toll-like receptors and interferon in innate immune responses, are also now recognized to be important in host defense against VZV^{62,63} as well as T cells.

Live attenuated varicella vaccine, latency and VZV reactivation

It was hoped that the live attenuated varicella vaccine would not cause either latent infection or zoster, but that has not turned out to be the case. In one study of 322 cases of zoster in vaccinated children whose VZVs were typed as either wild virus or the Oka (vaccine) strain, 50% of cases were due to the wild type virus.⁶⁴ Presumably these children had been infected subclinically with wild type VZV, perhaps after receiving only 1 dose of vaccine, and developed latent infections at that time from natural VZV. However the incidence of zoster was 5 times lower in vaccinated children than in a group of controls who were not immunized and who had experienced natural varicella infection. There was no difference in the clinical severity of zoster caused by the Oka strain and wild type VZV. In vaccinees zoster occurred commonly, but not exclusively in the extremity into which the vaccine had been administered.⁶⁴

It has been recognized for many years that VZV infection of the skin during varicella could lead to latent infection of neurons, from which the virus could reactivate to cause zoster, usually with a unilateral rash. However, it was only after vaccination became common, that it was realized that VZV could establish latency by infection of neurons during the cell-associated viremia of varicella. An example would be when Oka zoster occurs in skin not

innervated by nerves at the injection site, such as the face or on the side opposite to the injection site.³ Latency can thus result when VZV is transferred directly to neurons from skin or by viremia in the presence or absence of a skin rash.

Importantly, a decrease in zoster rates following vaccination as compared to natural infection has been observed not only in children but also in adults. In one study the incidence in healthy adult vaccinees was 0.9/1000 person years (P-Y) of observation; after natural infection the incidence in similarly aged healthy adults is 2–3/1000 P-Y.⁶⁵ The pressing question now is whether the incidence of zoster will increase among individuals who have not been vaccinated but have experienced natural varicella in the absence of natural re-exposure to circulating varicella.

Will the incidence of zoster increase in the unvaccinated as a result of the widespread use of live attenuated varicella vaccine?

It was hypothesized in 1992, that circulating wild type VZV in the population is critical for the long-term maintenance of immunity to VZV, particularly for the prevention of reactivation of the virus.⁶⁶ Subsequently in 2002, a study utilizing computer modeling predicted that there could be an extra 21 million cases of zoster and 5000 deaths, in countries with universal vaccination.⁶⁷ In part because of such concerns, a number of countries, including Britain, therefore did not implement universal varicella vaccination in children. Now almost 15 years later, the predicted accelerated rise in incidence has not been observed in the USA after prolonged high-coverage varicella vaccine usage and mechanisms of long-term immunity to VZV are being rethought.

It is recognized that the incidence of zoster is on the rise, but this increase began in the middle of the 20th century, long before development or use of varicella vaccine. Therefore observed increases in the incidence of zoster cannot be due to use of varicella vaccine alone. Moreover increases in zoster have occurred both in countries where vaccine use is common and in others where the vaccine is not used. The increase is probably multifactorial and includes increased identification of the disease (ascertainment), increasing numbers and proportions of elderly people and immunocompromised individuals in many countries, and rising stress levels, which also seems to cause reactivation of VZV. Stress was identified a risk factor by studies in astronauts returning from space flights, in whom 30% had evidence of subclinical reactivation of VZV as evidenced by the transitory presence of VZV DNA in their saliva.⁶⁸ The trajectory of the increase in the rate of zoster in US populations was not affected by the introduction of varicella vaccine.⁶⁹

Hope-Simpson, in 1965, who first recognized that zoster is mainly a disease of the aged, postulated that exogenous exposure to VZV could boost protective immunity to the virus, but he also theorized that subclinical reactivation of VZV, which he referred to as “contained reversions,” occurred and could also boost immunity.⁴³ The investigators who postulated that there would be an epidemic of zoster due to a decrease in external exposure to circulating VZV did not take into account the possibility of internal exposure to reactivated VZV.^{66,67} Evidence of asymptomatic reactivation of VZV was identified beginning in the late 1970s, in the form of asymptomatic increases of VZV antibodies and cellular immunity

that occurred in healthy and immunocompromised individuals.⁷⁰ In some instances patients with asymptomatic VZV reactivation were identified by the transient presence of VZV DNA by polymerase chain reaction (PCR), in blood and in saliva.^{71–76} Asymptomatic women who have passed VZV to their infants at delivery with development of VZV symptoms in the baby soon after birth have also been described.^{77,78} One especially interesting study of cloistered nuns and monks demonstrated that the incidence of zoster (~15%) was similar over a 30 year period to the incidence in the general population during the same time; while only the latter were exposed to individuals with varicella.⁷⁹ Since the rates of zoster were the same for both groups, exposure to VZV is unlikely to be required to maintain immunity against development of zoster. In summary, with the extensive evidence of asymptomatic reactivation of VZV, and the epidemiologic information cited, it seems safe to say that widespread use of varicella vaccine would not be expected to lead to an increase in zoster in populations of adults who had experienced natural varicella in the past.

Vaccination against zoster

The live attenuated zoster vaccine, which was licensed 11 years ago in the United States and contains 14 times the amount of vaccine (Oka) VZV contained in varicella vaccine, has proven to be very successful in preventing zoster.⁸⁰ In contrast to the preventive varicella vaccine, live attenuated zoster vaccine is a therapeutic vaccine that prevents disease in those harboring latent infection by boosting cellular immunity to VZV. It prevents zoster and thereby post herpetic neuralgia (PHN) in ~60% of healthy 60 year olds. Its efficacy may be even better when given to 50 year olds.⁸¹ It is a very safe vaccine, but is not used in immunocompromised patients. In addition booster doses may be necessary after 8 years.⁸² This vaccine is an outstanding proof of concept vaccine for zoster prevention, but there is room for improvement.

A potentially more successful vaccine against zoster was developed recently; it is an adjuvanted subunit VZV vaccine, composed of VZV gE and the AS01B adjuvant, which improves both CD8 and innate immune responses.^{83,84} Its protective efficacy in a phase 3 double blind study was over 95% even in individuals over age 70.⁸⁵ It has also been studied in phase 2 trials in immunocompromised patients, in whom it shows great promise.⁸⁶ Licensure of this vaccine for healthy elderly persons is currently under consideration in the US.

Conclusions

It is clear that VZV infections are potentially severe, and that safe and effective approaches to prevent and treat them are needed. Viral transmission is reduced by use of varicella vaccine in children. However, the effects of decreases in transmission of VZV are complicated by viral latency in and reactivation from dorsal root ganglia, cranial nerve ganglia, and enteric and other autonomic ganglia. Much zoster can potentially be prevented by immunization of varicella-immune adults, further reducing the circulation of virus in the population. Judicious use of safe and effective VZV vaccines seems to offer the greatest promise as an approach to controlling the problems caused by this virus.

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