Journal of Infection (2017) 74, S27—S33

BIA
British Infection Association

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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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Available online 23 June 2017

KEYWORDS
Varicella;
Chickenpox;
Zoster;
Vaccination;
Latency;
Reactivation

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.

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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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 offspring 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.