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Mark Cotton developed an interest in infectious diseases while specialising in paediatrics at the University of the Witwatersrand, largely through contact with Dr Frank Berkowitz. After moving to Stellenbosch University, he completed a fellowship in Paediatric Infectious Diseases at the University of Colorado Health Science Centre, Denver, Colorado. On return to Tygerberg Children's Hospital, he has spent most of his time working on HIV-related issues in children.

The varicella zoster vaccine

Chicken pox is generally thought of as a trivial childhood illness. But it can have serious consequences in immunocompromised people. Hence the importance of the vaccine.

EPIDEMIOLOGY

Chicken pox (varicella) is erroneously regarded as a trivial, self-limited infection of children. While the death rate in children is below 2/100 000, it rises more than 15-fold in adults.[1] Prior to the introduction of antiviral medication, the mortality rate in leukaemic children was 7%, 3 500-fold higher than in immunocompetent children.[2]

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Ninety per cent of cases of chicken pox occur in children younger than 13 years of age. However, 10% of adolescents and adults are still susceptible to varicella. For example, Waner showed that 10% of medical students attending the University of the Witwatersrand were susceptible.[3]

PATHOGENESIS

Chicken pox is caused by the varicella zoster virus (VZV) and is closely related to herpes simplex, that causes cold sores and genital ulcers. An important characteristic of VZV is that it is very efficiently spread by airborne microscopic droplets or by contact with infected secretions. The incubation period usually varies from 14 to 16 days although the range is 10 - 21 days. In patients who have received varicella zoster immunoglobulin (VZIG), the incubation period is extended to 28 days.

NATURAL HISTORY

Varicella usually presents with a short history of fever for 1 or 2 days followed by crops of skin lesions on the trunk. The skin lesions characteristically start as red spots, rapidly become vesicles (blisters) and then form crusts. The rash is often very itchy. The blisters are described as 'dewdrops on petal'. A characteristic feature of the rash is that at any one time, the skin lesions will be present in various stages. Occasionally the blisters occur in the mouth as well. Usually, by day 3 - 5, no new blisters are seen. For those interested in counting blisters, between 250 and 500 lesions are seen in an 'average' infection. The child is infectious from the time of feeling ill until the last blister has formed a crust. Knowledge of the natural history of chicken pox is important as any deviation may suggest life-threatening complications, where rapid recognition and early intervention favourably alter the course of events.

COMPLICATIONS

Large surveys of normal infants and children show a small but significant rate of complications. For example, in a recent German survey of children below 16 years of age, 8/100 000 had illness severe

enough for hospitalisation.[4] The majority were central nervous system sequelae such as postinfective cerebellar ataxia that resolved without sequelae. However, secondary bacterial infections due to *Staphylococcus aureus* and *Streptococcus pyogenes* were responsible for more than a third of serious complications that include necrotising fasciitis and disseminated multifocal osteoarthritis. In adults, varicella pneumonitis and acute encephalitis are two common and potentially fatal complications. In immunocompromised patients, progressive varicella can occur, characterised by continuing eruption of lesions and high fever into the second week of the illness. This may progress to encephalitis, hepatitis or pneumonia. Haemorrhagic chicken pox is also more common in immunocompromised patients.[5]

Even the treatment of chicken pox can be problematic. Where aspirin is used for temperature control, a severe and often fatal metabolic disease called Reye's syndrome can occur. This condition manifests as excessive vomiting and decreased level of consciousness. Other non-steroidal anti-inflammatory agents have also been implicated in complicated varicella.[5] For these reasons, only paracetamol should be used as an antipyretic agent.

There is an appreciable risk for congenital anomalies when varicella occurs in the first half of pregnancy. The incidence of congenital varicella syndrome following from exposure between zero and 12 weeks is 0.4% and rises to 2% following exposure between 12 and 20 weeks' gestation. The congenital varicella syndrome includes anomalies such as limb deformities, scars on the skin and chorioretinitis.

Table I. Patients at high risk for complications of disseminated varicella

- **Pregnant women**
- **Neonate born to woman who develops varicella between 5 days antepartum and 2 days postpartum**
- **Immunocompromised patients**
- **Adults**
- **Patients taking corticosteroids during the incubation period of varicella (2 mg/kg/day)**

Patients at high risk for complications of chicken pox (Table I)

Pregnant women are at risk for serious disease. Even more serious is the risk of severe chicken pox in newborn infants where the mother has developed symptoms in the days just before or after the birth of the infant.

There is no evidence that immunisation during the incubation period exacerbates the clinical course.[5]

In patients of all ages with depressed immunity, chicken pox is a very serious illness. Individuals on corticosteroids and cancer treatment are at especially high risk. HIV infection is also associated with severe chicken pox.

VZV VACCINE

Because of the high mortality in children with cancer, Takahashi and colleagues developed the attenuated Oka vaccine strain in the early seventies.[6] This strain was shown to be safe, effective and immunogenic in both immunocompromised and immunocompetent children and adults.[7,8] In the USA it has been used since 1995 and has caused a dramatic reduction in hospitalisation due to VZV. The vaccine was introduced in South Africa in March 2002. It may be administered at the same time as the MMR vaccine, but must be given at a separate injection site. If not given with the MMR, then there should be at least 4 weeks' gap between the two vaccines.

Storage

Storage under optimal conditions is important, and the 'cold chain' should be maintained. The lyophillised vaccine should be refrigerated. Once reconstituted, the vaccine should be administered within 30 minutes.

Indications for the use of the varicella vaccine

Indications for the vaccine's use are shown in Table II and cover both immunocompetent and immunodeficient patients. Because varicella causes a trivial disease in the majority of children, there is some debate as to whether all children should receive the vaccine or whether it should be reserved for high-risk situations. In USA, the vaccine is recommended for all infants at 12 months of age. Its use has been associated with a steady drop in hospitalisations due to chicken pox.[9] Cost benefit analyses favour widespread use of the vaccine.[10] Regrettably, the vaccine is not yet an option in public clinics in South Africa because of cost constraints.

Another argument against the use of the vaccine is concern that the duration of protection after the

Table II. Indications for and frequency of adminstration of Varicella zoster vaccine

Immune status	Group	Dosage	Comments
Healthy	Infants from 9 months of age*	1 dose	If given with measles mumps rubella (MMR) vaccine, use separate syringe and site or give 4 weeks apart Can be given at same time as other vaccines
	Adolescents and young adults Adults – give priority to: • Settings where VZV exposure is likely (teachers, day care workers) • Settings where rapid spread is likely (military, correctional facilities, students) • non-pregnant women of childbearing age • adolescents and adults in households with susceptible children	2 doses 4 - 8 weeks apart	
Immunocompromised	Acute lymphocytic leukaemia		In maintenance phase (withhold therapy in preceding week) Lymphocyte count > 0.7 X 10^9/l (children) and > 1200 X 10^9/l in adults and platelet count > 100 X 10^9/l
	HIV infection in children (no recommendation for adults)	2 doses 3 months apart	CD4 percentage > 25%
	Corticosteroids		If receiving < 2mg/kg/day or 20 mg/day if body weight > 10 kg If on higher dose for 14 days, reduce dosage & immunise after 1 month

*In USA vaccination is recommended from 12 months.

vaccine may be less than that of 'natural' chicken pox.There is also concern that, with gradual introduction of the vaccine and decreased circulation of the wild virus, fewer young children will get chicken pox and will thus be susceptible when older and at risk for more severe disease. As mentioned earlier, a small number of normal children do get serious complications following chicken pox.This is only evident if statistics are collected at a community level as even in the experience of individual doctors, few patients with severe disease are seen.

Post-exposure prophylaxis

VZV vaccine can prevent chicken pox if given within 72 hours and possibly up to 120 hours of known exposure to someone with chicken pox. If the exposure of the vaccinated contact occurred at the same time as the index patient, chicken pox may still occur, but this should not be regarded as a vaccine failure.There is no evidence that immunisation during the incubation period exacerbates the clinical course.[5]

The VZV vaccine results in long-lasting immunity in contrast to VZIG, which protects for only 2 weeks.

Should older patients routinely undergo serological testing prior to immunisation?

Serological testing is unnecessary in patients with a reliable history of chicken pox and between 70% and 90% of adults without a reliable history will also be immune. It may be cost-effective to screen adults with an unreliable history, but this will involve an extra health care visit.

Minor injection site reactions are common.

Vaccine efficacy

The vaccine is 85 - 90% effective in preventing varicella during an outbreak and 100% effective at preventing severe disease. 'Break through' varicella does occur in a small percentage of vaccinees, but is generally extremely mild with very few vesicles, which may be mistaken for insect bites.

How long does immunity last after VZV vaccine administration?

Studies from Japan show protection for 20 years and in the USA for 11 years. However, presence of wild-type varicella in the community may play a role by boosting immunity. This phenomenon would be expected to decline with more widespread use of the vaccine. Additional follow-up studies are necessary, although other live virus vaccines such as measles and rubella do give life-long immunity.[5]

Adverse events

Minor injection site reactions are common. A mild localised or generalised varicella-like eruption occurs in 3 - 5% of children within 4 weeks of receiving the vaccine. More serious short-term events have been rarely reported and difficult to link causally to the vaccine. In the longer term, the varicella vaccine can cause shingles in both immunocompetent and immunocompromised persons but this appears to occur at a much lower rate than shingles following natural varicella infection.

Contraindications

The vaccine should not be given to any significantly immunocompromised person (see Table II for guidelines). Transmission of the vaccine virus from a vaccinee to susceptible individuals is an extremely rare event and the virus remains attenuated so that an immunocompromised household member is not a contraindication to vaccination.

Varicella has not received appropriate recognition as a serious disease in South Africa.

As with all live virus vaccines, pregnant women should not be immunised and pregnancy should be excluded before immunising women of childbearing age. Women should avoid conception in the month after vaccination. The manufacturer of the vaccine and the Centers for Disease Control, USA, jointly maintain a registry for women inadvertently immunised during pregnancy. There is also a theoretical risk of transferring virus through breast milk but a breast-feeding mother should be immunised if there is chicken pox exposure.

The vaccine should not be given to persons who have had anaphylactic-type reactions to constituents of the vaccine, including gelatin and neomycin.

CONCLUSION

Varicella has not received appropriate recognition as a serious disease in South Africa. The VZV vaccine represents a major advance in clinical care. Cost constraints are a serious impediment to widespread use.

References available on request.

IN A NUTSHELL

Although chicken pox is regarded as a trivial infection of childhood, it can have serious consequences in immunocompromised patients, all adolescents and adults, and in a minority of immunocompetent children.

For HIV infection, at present, a CD4 percentage > 25% is recommended before vaccination.

The varicella vaccine, consisting of live attenuated virus, is safe and effective.

It can be given to infants from 9 months of age, but is probably better to give at 12 months.

All susceptible adults and adolescents should be immunised, especially where the risk of contact is high (health care and day care workers and parents with young children).

The vaccine is effective as post-exposure prophylaxis if given within 72 hours of exposure.