THE NORTHERN HOSPITAL

HERPES ZOSTER (SHINGLES)

"The Entry of Mehmet II into Constantinople", oil on canvas, Benjamin Constant, 1876.

"The number of the Ottomans was fifty, perhaps one hundred, times superior to that of the Christians; the double walls were reduced by the cannon to a heap of ruins: in a circuit of several miles, some places must be found more easy of access, or more feebly guarded; and if the besiegers could penetrate in a single point, the whole city was irrevocably lost. The first who deserved the Sultan's reward was Hassan the Janissary, of gigantic stature and strength. With his scimitar in one hand and his buckler in the other, he ascended the outer fortification: of the thirty Janissaries who were emulous of his valour, eighteen perished in the bold adventure. Hassan and his twelve companions reached the summit: the giant was precipitated from the rampart: he rose on one knee, and was again oppressed by a shower of darts and stones. But his success had proved that the achievement was possible: the walls and towers were instantly covered with a swarm of Turks; and the Greeks, now driven from the vantage ground, were overwhelmed by increasing multitudes. Amidst these multitudes, the emperor who accomplished all the duties of a general and a soldier, was long seen and finally lost. The nobles, who fought round his person, sustained, till their last breath, the honourable names of, Palaeologus and Cantacuzene: his mournful exclamation was heard, "Cannot there be found a Christian, to cut off my head?" and his last fear was that of falling alive into the hands of the infidels. The prudent despair of Constantine cast away the purple: amidst the tumult he fell by an unknown hand, and his body was buried under a mountain of the slain. After his death resistance and order were no more: the Greeks fled towards the city, and many were pressed and stifled in the narrow pass of the gate of St. Romanus. The victorious Turks rushed through the breaches of the inner wall; and as they advanced into the streets, they were soon joined by their brethren, who had forced the gate Phenar on the side of the harbour. In the first heat of the pursuit about two thousand Christians were put to the sword, but avarice soon prevailed over cruelty; and the victors acknowledged that they should have immediately given quarter, if the valour of the emperor and his chosen bands had not prepared them for similar opposition in every part of the capitol. It was thus, after a siege of fifty three days, that Constantinople, which had defied the power of Chosroes, the Chagan, and the Caliphs, was irretrievably subdued by the arms of Mehmet the Second. Her empire had only been subverted by the Latins; her religion was trampled in the dust by the Moslem conquerors".

Edward Gibbon ,
The Decline and Fall of the Roman Empire,
Volume VI, 1787.

On the 29th of May 1453, the Ottoman Turks stormed through a breach in the great walls of Constantinople and put the city to the sword. The walls which had stood for over a thousand years had protected the city against all invaders had finally succumbed to the new weapons of the age - the cannon and gunpowder. Although Constantinople had been in long decline and decay for over 250 years, since its sack at the hands of the Fourth Crusade in 1204, the final end came as severe shock to Christendom. The Byzantine empire, in unbroken lineage, heir to the Eastern Roman Empire, in turn heir to Imperial Rome, in turn heir to the Roman Republic in turn heir to the very foundation of Rome by, according to legend, Romulus in 753 B.C - had finally succumbed to the Turk.

Even though the once great city of Constantine I, by 1453, was the merest shadow of its former greatness, it's symbolic meaning at least was powerful and clear to all Christians and

Muslims alike. The great Sultan Mehmet II, whose lands surrounded the city on all sides and who merely tolerated it on account of its impregnable walls was finally given the ability to destroy it by means of the cannon. Given the long history of Byzantine corruption, treachery, licentiousness, brutality, and infighting one would have expected a very inglorious end when it came. But in complete contrast to the shameful fall of the Western Roman Empire in 475 AD in a bloodless coup by a barbarian general who outed the young, poignantly named Romulus Augustus, - the final fall of the Greco-Roman lineage was heroic in the extreme and the last Emperor Constantine XI would die in a manner that Augustus Caesar himself would have applauded.

As swarms of Turks surged through the breach in the walls, Constantine realising that the city was now lost vowed not to be taken alive by the infidel. He implored the members of his Imperial Guard to kill him on the spot - but none could bring themselves to lay a hand against the Emperor. Constantine, then discarded his Imperial robes and all insignia that could identify him as the Emperor, and took on the clothes of a common solder, and with sword in hand joined the last of his troops in a charge against the Turkish hoards. He died magnificently as a common soldier defending the city and lay dead under a mountain of corpses - his body was never indentified. He became legend - still revered by Greeks, even today.

Numerous legends in fact sprang up about the last heroic Emperor of Rome, but the most popular of all was that of the sleeping "marble emperor". It was said that he had not died, but that an angel of God had swept him up amidst the tumult of battle and turned him into a marble statue which was then concealed in a subterranean cavern near the Golden Gate. There the marble emperor sleeps until such time as the sins of the Byzantines have been atoned, (…a rather long wait - one suspects). Only then will the angel awaken the emperor who will expel the Turk from the city to a place far away marked by a red apple tree. The angel also turned the patriarch into marble while has was reciting the liturgy in Saint Sophia as the Turks stormed into the great Church. There he also lies in marble, awaiting the day when he will be released with the emperor and complete his interrupted liturgy.

In 1625 the British ambassador to the Porte, at Constantinople Sir Thomas Roe was attempting to remove some ancient statuary to send to the Duke of Buckingham for his collection of antiquities, when he observed that the old Golden gate had been walled up, "since the time of the Greek Emperors". He failed in his bid to remove the statuary not so much from official Turkish intervention, as from a superstitious dread of the local people. His interpreter told him that there was a prophecy that the statues were enchanted and that if they were taken down, a great disaster would befall the city. Sir Thomas reported his failure to the Duke…"He spake of a vault underground, that I understand not...and it is true that, though I could not get the stones, yet I almost raised an insurrection in that part of the city".

Many viruses are overwhelmed and defeated by the immune system. Yet in some cases that is not the end of the story. Some like the varicella virus may, like the marble emperor of legend, lie in wait - dormant - only to re-awaken and seek vengeance many years later.

HERPES ZOSTER (SHINGLES)

Introduction

Herpes zoster (shingles) is a common problem.

Treatment is usually straight forward in uncomplicated cases, but complicated cases such as shingles in **pregnancy** or in the **immunocompromised** represents potentially serious disease and treatment can be very complex and so will require specialist advice.

See also separate documents on:

- **Chickenpox (in Infectious Diseases folder)**
- **Herpetic Eye Disease (in Ophthalmology folder)**
- **Ramsay Hunt syndrome (in Neurology folder).**

Epidemiology

The incidence of shingles increases with age and children under 12 are rarely affected unless immunosuppressed or infected as infants in the first 2 years of life if there has been a history of maternal varicella.

Herpes zoster (shingles) occurs in 20% of people, mostly when they are elderly due to the reactivation of latent virus from the dorsal root ganglia.

Pathology

Organism:

The causative agent is the **varicella zoster virus (VZV)** (also known as human herpes-virus 3 (HHV-3)

Following primary infection with varicella-zoster virus (VZV), which causes **chickenpox** in susceptible hosts, latent infection is established in the sensory dorsal root ganglia of neurons.

Reactivation of endogenous latent VZV infection within the sensory ganglia results in herpes zoster or “shingles”, a syndrome characterized by a painful, unilateral vesicular eruption in a restricted dermatomal distribution.

Reactivation occurs in about 15 - 30 per % of infected persons during their lifetime, resulting in herpes zoster (shingles). [1]

This can be a serious disease in the elderly and in the immunocompromised and when particular nerve distributions are affected, (such as the Ophthalmic or the Vestibulocochlear or Facial nerves)

Complications:

Complications of herpes zoster include:

1. Herpes zoster ophthalmicus with ocular involvement

2. Auditory Nerve or Facial Nerve involvement (Ramsay Hunt syndrome **see separate document in Neurology folder**).

3. Disseminated herpes zoster, (in the immunocompromised).

    - Disseminated herpes zoster is a form of shingles characterized by skin lesions outside the affected dermatome, and or with potential involvement of other organs (for example, causing hepatitis or encephalitis).

4. Secondary bacterial infection.

5. Varicella zoster or chickenpox in pregnancy and the newborn: [1]

    Pregnancy:

    Specialist advice is essential in these cases.

    - Varicella infection during the first trimester of pregnancy confers a small risk of miscarriage.

    - Maternal infection before 20 weeks may rarely result in the foetal varicella zoster syndrome, with the highest risk (2%) occurring at 13- 20 weeks.

    - Clinical manifestations include growth retardation, cutaneous scarring, limb hypoplasia and cortical atrophy of the brain.

    - Intrauterine infection can also result in herpes zoster in infancy. This occurs in less than 2% of infants. The highest risk is associated with infection in late pregnancy.

    - In the third trimester, maternal varicella may precipitate the onset of premature labour.

    - Severe maternal varicella and pneumonia at any stage of pregnancy can cause foetal death.

    - Susceptible pregnant women who have been exposed during pregnancy should seek specialist obstetric advice. They may be offered zoster immune globulin (VZIG) and antivirals (famciclovir, valaciclovir or aciclovir), especially where delivery is imminent.

- Where chickenpox develops in pregnancy, early medical review within 24 hours of rash onset is indicated to consider treatment options.

Newborns:

Specialist advice is essential in these cases.

- Where newborns develop varicella before ten days of age or when maternal chickenpox develops within seven days prior to delivery and up to 48 hours postpartum, the neonatal fatality rate is up to 30% without treatment.

- Treatment of mothers and of babies once born is vital.

- Premature babies and infants less than one month old who develop varicella may require specific treatment.

6. Post herpetic neuralgia:

- A debilitating complication of herpes zoster in many (especially elderly) patients is prolonged pain (post-herpetic neuralgia) which may persist for months after resolution of the skin lesions.

Reservoir

- Humans.

Period of communicability

- Chickenpox is usually communicable for one to two days (up to five days) before the onset of the rash, continuing until all the lesions are crusted. Communicability may be prolonged in patients with altered immunity.

- Those with **zoster** are considered infectious for a week after lesions appear when they are moist.

Susceptibility and Resistance

- Whilst chickenpox is highly infectious, herpes zoster much less so.

- Over 80% of non-immune household contacts of a case of chickenpox will become infected. Non-immune people exposed to shingles cases will develop chickenpox (not zoster) if they become infected.

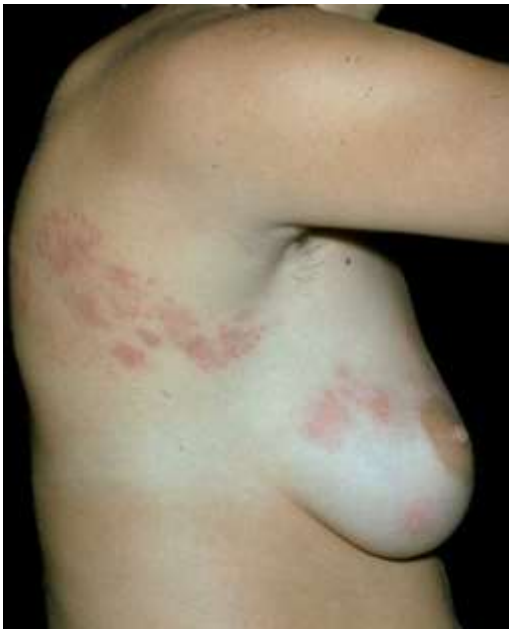
- Second attacks of chickenpox are rare but do occur.

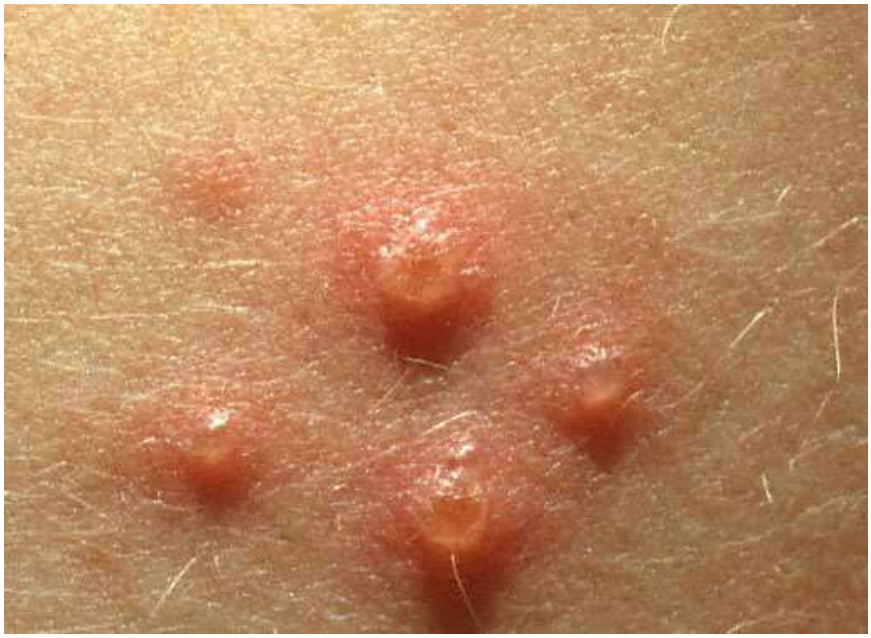
- **Infection remains latent and can recur years later as shingles.**

Patients who are at **high risk** of severe disease/complications if they do not have immunity include:

- **Infants (less than one month old).**
- **Pregnant women**
- **Immunosuppressed individuals including those with haematological malignancies, on chemotherapy, high dose steroids or with HIV infection.**

Clinical Features





Left: Typical dermatomal distribution of herpes zoster. Right: Typical fluid filled vesicular lesions of chickenpox/ herpes zoster.

Clinical features of herpes zoster infection include:

1. Non-specific constitutional symptoms:

   These may include:

   - Fever
   - Malaise/ lethargy

2. Rash:

   - Herpes zoster (shingles) is characterized by a **vesicular** eruption on an erythematous base

- The rash lies within a **unilateral** *and* **dermatomal** distribution.
- There are often groups (or "crops") of vesicles
- It is often associated with severe pain that may *precede* lesions by **48 - 72 hours.**
- In *general* the blisters erupt over **1 week** and then heal with crusting over **2 weeks**, but may take longer depending on severity.
- The rash is often more widespread and persistent in **immunosuppressed** patients. It may even become generalized.

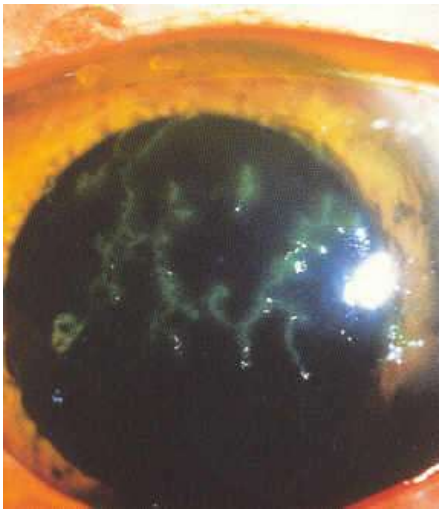
3. Ocular Involvement:

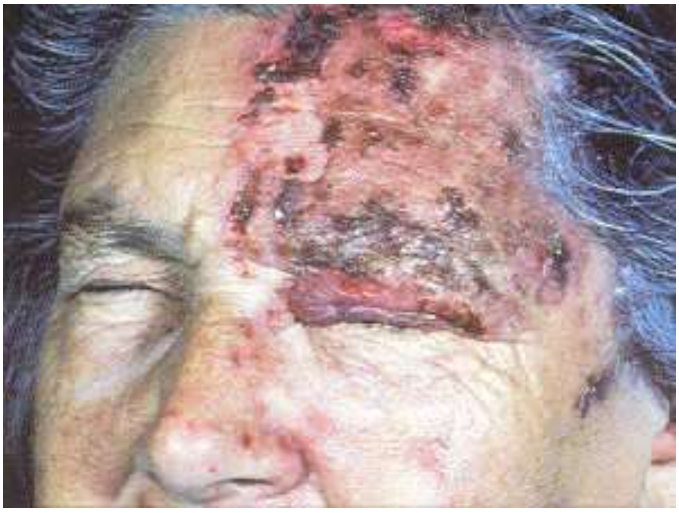
   Patients must be carefully evaluated to ensure that there is no eye involvement when the rash involves the ophthalmic area of the face.

   Lesions on the cornea:

   - These appear as dendritic ulcers with branching arms.
   - They are readily seen on fluorescein staining of the cornea.

4. Nasociliary nerve involvement:





Left: Typical dendritic ulcers of varicalla-zoster virus seen on fluorescein staining. Right: Nasal involment due to infection within the Nasociliary nerve, indicating probable ocular involvement.

- Lesions found on the nose indicate involvement of the nasociliary nerve. If this is found there is high likelihood of ocular involvement.

5. Post-herpetic neuralgia:

   - The pain of postherpetic neuralgia is usually severe.
   - It may present as burning aching boring pain, or it may present as paroxysmal shock-like stabbing or lancinating pain.
   - Ninety % of patients have severe pain to a light dynamic mechanical stimulus, such as gentle brushing of the skin (allodynia) despite sensory loss to routine examination.
   - Hyperpathia occurs less commonly.

See also appendix 1 below for description of neuropathic pain in general

Investigations

None are routinely necessary in clear cut cases, as the diagnosis can usually be made on clinical grounds.

Confirmation of the diagnosis is therefore generally only required when the clinical picture is atypical.

It can be confirmed by:

1. Serological tests for antibodies:

   - IgM antibody, (acute infection)
   - IgG antibody, (past infection)

2. PCR testing:

   - Vesicular fluid can be tested.

3. Isolation of the virus in cell cultures and visualization by electron microscopy can also be done on lesion fluid.

Management

Herpes Zoster therapy and associated pain management should be treated early and aggressively as it is more difficult to treat once established.

In uncomplicated cases:

1. **Analgesia**:

For mild to moderate pain:

- Paracetamol 1gram orally 4 hourly prn (to a maximum dose of 4 gram per 24 hour period.

  If the oral route is contraindicated, paracetamol can be given IV 1gram 6 hourly.

And/or:

- Aspirin 300 - 600mg orally 4 hourly prn

With or without:

- Oxycodone 5 to 10mg orally 6 hourly prn

For severe pain:

To the above consider adding:

- Prednisolone 50 mg orally once daily for 7 days, then tapered over 14 days

And/or:

- Amitriptyline 10 mg to 25 mg orally nocte initially; titrate up to a maximum nocte dose of 150mg

2. **Antiviral treatment:**

Antiviral treatment is indicated in:

- Patients seen within **72 hours** of the onset of vesicles.
- All **immunocompromised** patients, (even **after 72 hours**)
- All patients with **ophthalmic** herpes zoster, (even **after 72 hours**)

Antiviral agents commenced within 72 hours of the rash have been shown to:

- Reduce duration of pain
- Reduce the duration of the rash
- Reduce ophthalmic complications.

Three options are currently available: [2]

There is evidence that famciclovir and valaciclovir are more effective than acyclovir in reducing acute pain in patients with herpes zoster.

Although there are more safety data to support the use of acyclovir in pregnancy compared with valaciclovir or famciclovir, there is some evidence and clinical experience that valaciclovir, a prodrug of acyclovir, is safe in pregnancy.

- **Famciclovir** 250 mg orally 8 hourly for 7 days

  If immunocompromised use 500 mg orally 8 hourly for 10 days

Or

- **Valaciclovir** 1gram orally 8 hourly for 7 days

Or

- **Acyclovir** 800 mg (child: 20 mg/kg up to 800 mg) orally, 5 times daily for 7 days.

See current edition of Therapeutic Guidelines for full prescribing details.

In complicated cases:

These cases will require specialist advice.

3. Ocular involvment:

   - Patients must be carefully evaluated to ensure that there is no eye involvement when the rash involves the ophthalmic area of the face.

   - **Specialist Ophthalmologist referral is mandatory in these cases as blindness can result.**

4. Varicella zoster in **high risk - immunocompromised** patients:

   - More intensive treatment is warranted in these high risk patients.

     Specialist advice should be sought for high risk patients, such as immunocompromised patients and pregnant patients, who contract varicella-zoster.

     In *general* terms, for **immunocompromised** patients with **disseminated disease**, admit to hospital for **IV acyclovir** therapy. [2]

Use:

Adults:

- Acyclovir 10 - 12.5 mg/kg IV, 8-hourly.

Child:

- 500 mg/m^2 (approximately 20 mg/kg for child 5 years or younger; 15 mg/kg for child 5 years or older) IV, 8-hourly

After significant clinical improvement, change to oral antiviral therapy (as above) to complete 7 days of treatment (IV + oral).

5. Post exposure prophylaxis:

Varicella vaccination:

- Vaccination may be used to prevent or attenuate illness if given to susceptible contacts within five days (preferably 72 hours) of first exposure.

Varicella zoster immunoglobulin (VZIG):

- High risk susceptible contacts where vaccination is not indicated such as neonates pregnancy and immunosuppressed persons should be offered varicella-zoster immune globulin (VZIG) within 96 hours of exposure. If vaccination is not contraindicated this should follow at least 3 months later.

See also current edition of the Australian Immunization Handbook, National Health and Medical Research Council, for full prescribing details.

Specialist advice should be sought in these cases.

Notification

- Notification is not required.

School exclusion

- Children with shingles can attend school if the lesions can be covered adequately however exclusion from swimming and contact sports should be advised for seven days after the rash appears.

Post herpetic neuralgia: [2]

Postherpetic neuralgia is pain persisting for longer than 4 to 6 weeks after crusting of the vesicles of acute herpes zoster (shingles).

It occurs in about 10% of all patients with herpes zoster, and up to 75% of those over 70 years of age.

Vaccination of adults has been shown to reduce the incidence and severity of zoster infection and postherpetic neuralgia, although hundreds of people need to be vaccinated to prevent one case of postherpetic neuralgia.

The pain of postherpetic neuralgia is usually severe.

It may present as burning, aching or boring pain, or as paroxysmal shock-like stabbing or lancinating pain.

Ninety per cent of patients have allodynia despite sensory loss to routine examination. Hyperpathia occurs less commonly.

The skin of the affected area may be depigmented and scarred, but the degree of scarring bears no relationship to the severity or quality of pain.

Postherpetic neuralgia is difficult to treat.

- It is largely a disease of the elderly, in whom consideration must always be given to problems associated with other diseases (particularly those affecting cognition) and to the maintenance of physical function and continued socialisation.

- Treatment should begin with the simplest and safest approaches, such as aspirin or paracetamol, ice massage, transcutaneous electrical nerve stimulation (TENS) or lignocaine.

- If these produce inadequate relief, try either a tricyclic antidepressant (TCA) (such as amitriptyline or nortriptyline) or an antiepileptic drug (such as pregabalin or gabapentin). If still unresponsive, it may then be reasonable to try oral opioids.

See Therapeutic Guidelines for full prescribing details.

Appendix 1

Neuropathic pain: [1]

Neuropathic pain occurs in a number of clinical conditions where there is peripheral or central nervous system damage or dysfunction.

Examples of **peripheral neuropathic pain** include conditions such as **post-herpetic neuralgia,** surgical trauma, diabetes, brachial plexus injury, limb amputation (eg phantom linb pain) and the various causes of axonal neuropathy.

Central neuropathic pain often occurs following spinal cord injury, stroke, and in multiple sclerosis.

Neuropathic pain is typically described as a constant burning, episodic shooting or electric pain in a region where there is a disturbance of sensory and/or motor function, particularly to pinprick and thermal (warm and cold) sensibility. It is characterised by spontaneous pain, and by abnormal evoked responses.

These include:

Hyperalgesia: An increased responsiveness to normally painful stimuli

Allodynia: A painful response to normally nonpainful stimuli

Hyperpathia: An abnormally painful reaction to a stimulus, especially a repetitive stimulus, with an increased threshold.

These sensory disturbances may spread outside recognised anatomic boundaries for nerves and receptor fields.

In contrast, the true neuralgias (eg trigeminal neuralgia) are not associated with a primary disturbance of sensation, have a slightly different pathogenesis, and respond to a different array of medication. For further information, see trigeminal neuralgia in Therapeutic guidelines.

Several mechanisms may be responsible for neuropathic pain. These include generation of ectopic impulses from damaged nerves, wind-up and long-term potentiation in central pathways, loss of the normal inhibitory processes at both spinal and supraspinal levels, and modification of activity through glial activation and neuronal apoptosis.

A recognition of the presence of central changes following nerve injury is important, as it probably underlies the poor response of treatments that are directed purely at the periphery or the site of injury

Emperor Constantine XI Palaeologus, bronze, Athens.

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1. Varicella Zoster in The Blue Book Website, Accessed September 2018.

2. eTG - July 2028

3. The Acute Pain Management Manual NHMRC, 2011.

4. Australian Immunization Handbook, 10th ed Website, Accessed September 2018.

    - https://immunisationhandbook.health.gov.au/

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Reviewed October 2018.