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Tropical Population Health Unit

Network

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COMMUNICABLE
DISEASE CONTROL

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THREE MORE MISSED CASES OF ACUTE RHEUMATIC FEVER

CASE 1:

A 12-year-old Indigenous girl presented to an Emergency Department at a hospital in north Queensland with fever, and an acute refusal to weight bear because of an increasingly painful L foot. There was a localised area of redness, swelling, warmth and tenderness over the inner aspect of the mid-foot; 'septic arthritis' and 'cellulitis' were considered. She was given a dose of intravenous ceftriaxone; blood for cultures (no pathogen isolated) and CRP (131 mg/L) was collected, and she was discharged.

She was still not weight bearing the next day. Although the ankle joint was considered to be normal, the mid-foot findings remained unchanged. She was considered to have 'cellulitis' and dispensed an oral antibiotic and an anti-inflammatory medication.

At no stage was a mid-tarsal inflammatory monoarthritis considered, nor was a paediatric opinion sought. She was not followed-up, but presented again about two months later with florid rheumatic chorea.

CASE 2:

A 7 1/2-year-old Indigenous boy was seen at an Aboriginal Medical Service with painful feet and torticollis. He did not present for a review, but three weeks later represented with a painful, swollen L knee. He also complained of being unwell with vague fevers and poor appetite. His ESR was 93 mm/hr, ASOT 885 IU/mL and antiDNaseB 928 IU/mL.

The next day there was a large effusion in the knee. He was referred with differential diagnoses of septic arthritis and acute rheumatic fever to the local hospital. On admission, a history of 'pain and swelling in the L knee four weeks ago, spread to both ankles, lasted a few days. Then developed pain in both hips, shoulder-neck which lasted a day or so two weeks ago. Then pain and swelling in L knee' was noted. He had a low grade fever.

The knee joint aspirate had $13,000 \times 10^6/L$ WBCs with 75% polymorphs, but no organisms were seen on gram stain or grown on culture. A diagnosis of 'reactive arthritis' was made.

Although it was noted (twice) that the case was to be discussed with a paediatrician, this did not occur. The discharge sheet was never completed, and there was no referral back to the Aboriginal Medical Service (so he was lost to follow-up).

A pathological systolic murmur was detected when he was admitted to a regional hospital 27 months later with acute post-streptococcal glomerulonephritis. Rheumatic heart disease was confirmed by echocardiography.

CASE 3:

A 4 1/2-year-old Indigenous girl was admitted to a local hospital with acute refusal to weight bear because of a painful L knee. She was also refusing to use her arm because of a painful R elbow. She was febrile; the elbow pain settled after a day but then her R wrist became painful. Her ESR was 77, CRP 104, ASOT 134 and antiDNaseB 224 IU/mL.

Acute rheumatic fever was considered but 'results do not indicate that she had that'. A follow-up appointment with repeat blood tests was arranged, but she did not attend the appointment. This case was 'found' by a visiting Public Health RN, who was examining the case notes for another reason.

COMMENTS

These three cases emphasise – again – the following key features of acute rheumatic fever as seen in north Queensland:

- School-aged (5-14 years of age) Indigenous children in north Queensland are at high-risk of developing ARF. (ARF can develop at a younger age, as seen in Case 3, but the majority of cases are in the 5-14 year age group.)



Sudden onset of refusal to weight bear is an ominous presenting complaint in an unwell Indigenous child.

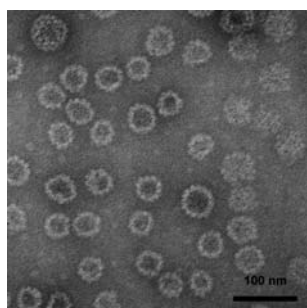
- Sudden onset of either refusal to weight bear or non-use of an upper limb (without an obvious cause) is an ominous presenting complaint in an unwell Indigenous child, as it often indicates an acute arthritis somewhere in the limb (as seen in Cases 1 & 3). ARF must be considered as a likely cause.
- Although the arthritis of acute rheumatic fever is usually described as involving multiple joints (polyarthritis), monoarthritis is not infrequently seen in Indigenous children in north Queensland (as seen in Case 2 upon admission, although the recent history indicated a polyarthritis).
- Septic arthritis should only be diagnosed following the isolation of a pathogen from a joint aspirate. An acutely inflamed joint in an Indigenous child with a sterile aspirate is almost certainly indicative of acute rheumatic fever.
- Carditis is rarely a presenting feature of ARF, and is not a mandatory criterion for the diagnosis of ARF.

FALSE CONTRAINDICATIONS TO HUMAN PAPILLOMAVIRUS VACCINE

CASE 1:

A 16-year-old high school student has multiple allergies, some apparently anaphylactic, to several food items including dairy products and eggs, and to some medications, including penicillin.

Based upon these anaphylactic sensitivities, her general practitioner advised her that she should not be given the human papillomavirus (HPV) vaccine.



Virus-like particles (VLPs) of one of the genotypes of HPV that is included in the vaccine

CASE 2:

A 17-year-old high school student developed 'a generalised itch, headache and nausea' several hours after being given a first dose of HPV vaccine.

Based upon this 'allergic reaction', her general practitioner advised that she should not have any further doses of the vaccine.

CASE 3:

A 26-year-old woman, in otherwise good health, developed faintness and light-headedness several hours after a first dose of HPV vaccine. She developed these same symptoms, dizziness and palpitations several hours after the second dose of the vaccine.

She did not seek immediate medical advice for either of these adverse events following immunisation. Nevertheless, on the basis of these 'reactions', her general practitioner advised her that she should not have the third dose of the vaccine.

DISCUSSION:

Not one of the above anaphylactic sensitivities, allergic reactions or reactions is a contraindication to HPV vaccine. Fortunately, the general practitioners were able

to be convinced to overturn their initial advice, and Case 1 subsequently received HPV vaccine, and Cases 2 and 3 further doses, without incident.

The 9th edition of The Australian Immunisation Handbook lists only two absolute contraindications to HPV vaccine:

- anaphylaxis to any vaccine component
- anaphylaxis following a previous dose of the vaccine.¹

This paucity of contraindications is a reflection upon the properties and constituents of the HPV vaccine. There are two different HPV vaccines registered for use in Australia, only one of which, a quadrivalent (4vHPV) vaccine, is currently being funded through the National HPV Vaccination Program.²

The HPV vaccines are not derived from HPVs harvested from tissue-cultures, but rather, they are synthesised using sophisticated molecular technologies. For example, to produce the 4vHPV vaccine, the gene which codes for a structural protein (L1 protein) in the outer shell-like "capsid" of the HPV, is 'spliced' into the DNA of bakers' yeast (*Saccharomyces cerevisiae*). This 'foreign' DNA causes the yeast cells to produce L1 protein from one particular genetic strain (genotype) of HPV. This protein is particularly important in the human immune response to HPV infection.³

The yeast-derived L1 protein has the intrinsic ability to self-assemble into 'pseudo-viruses' referred to as virus-like particles (VLPs).³ These VLPs are essentially 'empty' shells, and the inner space does not contain any HPV DNA. The 4vHPV vaccine is then made by mixing together minute amounts of VLPs made up of L1 protein from the four different genotypes (HPV6, 11, 16 and 18).

As they do not contain any viral DNA, the HPV vaccines are not live virus vaccines. This means that systemic adverse events following immunisation, such as fever, nausea and myalgia, are not likely to be of clinical concern following HPV vaccination. Indeed, these (and other) systemic adverse events occurred in almost equal percentages of vaccine and

placebo recipients in clinical trials.⁴ For example, 'dizziness' occurred in 4% of those who received 4vHPV vaccine compared to 3.7% of those who received placebo.⁴

However, as with almost all other non-live vaccines, HPV vaccines contain an adjuvant to enhance the immune response to the vaccine. For example, 4vHPV vaccine contains an aluminium adjuvant, which is recognised as contributing to a mild inflammatory response at the injection site. Therefore, in contrast to systemic adverse events which are not increased, local (injection site) adverse events following HPV vaccine can be expected. Indeed, in the 4vHPV vaccine clinical trials, the percentages of vaccine recipients with injection site pain (mostly mild to moderate in reported intensity), swelling and redness were all increased in the 1-5 days after the injection compared to those given a placebo injection.⁴ (There are also anecdotal reports of 'stinging' at the injection site immediately after injection with 4vHPV vaccine, but this has not yet been systematically studied.)

As well as the VLPs and the aluminium adjuvant, 4vHPV vaccine contains histidine (an amino acid buffer) to control the pH of the vaccine, and polysorbate 80 (a fatty acid ester) to stabilise the VLPs during the manufacturing process. It also contains sodium borate (a buffer) that stabilises the pH of the aluminium adjuvant prior to VLP adsorption, and it may contain a minute amount of yeast protein, as a residue of the production of L1 protein. The HPV vaccines do not contain preservatives or antibiotics.

An anaphylactic sensitivity to any vaccine component is a contraindication to HPV vaccine,¹ but the only component which could conceivably lead to a contraindication to 4vHPV is the possibility of a trace amount of yeast protein. However, extensive experience with hepatitis B vaccines, which also involve yeast to produce an essential hepatitis B virus protein, gives reassurance that yeast-derived vaccines pose an extremely low, almost negligible, risk even in those with some sort of yeast sensitivity.⁵ Regardless, if a person reports an anaphylactic sensitivity to yeast, 4vHPV vaccine is contraindicated. In this situation, the bivalent HPV (2vHPV) vaccine should be used instead, as the production of 2vHPV vaccine does not involve yeast. (NB: 2vHPV vaccine is not currently funded through the National HPV Vaccination Program.)

In summary, anaphylactic sensitivities to non-vaccine components, mild allergic adverse events and mild systemic adverse events are not contraindications to HPV vaccination. The only plausible contraindication to the 4vHPV vaccine is an anaphylactic sensitivity to yeast. Local (injection site) adverse events, usually mild, can be expected to occur following HPV vaccines, but because they are not live virus vaccines, they are not associated with an increase in systemic adverse events. The only contraindication to further doses is anaphylaxis following a previous dose.

General practitioners, indeed all immunisation service providers, should never recommend that HPV vaccine is

contraindicated without seeking further advice from a physician with expertise in immunisation.

KEY POINTS

- There are very few true contraindications to HPV vaccines.
- An anaphylactic sensitivity to yeast is a contraindication to 4vHPV vaccine. In this situation, 2vHPV vaccine should be used instead.
- Anaphylactic sensitivities to non-vaccine components, allergic and systemic adverse events that are not anaphylactic in nature are not contraindications to HPV vaccination.
- Immunisation service providers should never recommend that HPV vaccine is contraindicated without seeking further advice from a physician with expertise in immunisation.

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VACCINE AS FURTHER PROTECTION FOR HOUSEHOLD CONTACTS OF PEOPLE WITH MENINGOCOCCAL DISEASE

Invasive meningococcal disease should be promptly notified to the Tropical Population Health Network by telephone on clinical suspicion. This rapid response is to help us to identify and protect contacts quickly and effectively. In addition to clearance antibiotics for selected close contacts, Australia has now adopted vaccination for household contacts if the index case's meningococcal illness was caused by a vaccine-preventable serogroup (strain) of the bacterium.

N. meningitidis is greatly feared because it can kill within hours from overwhelming septicaemia in particular. A petechial rash may or may not be present. The disease usually occurs sporadically, but secondary cases and clusters can certainly occur, so there is always concern that further cases are imminent. Public health responses must be informed by the epidemiology of the organism – so, what are the risks, and what is the evidence for treating contacts with antibiotics and vaccines?

Meningococci colonise the nasopharynx in up to 10% of the population. They spread by respiratory droplets and close contact, yet less than 1% of those infected progress to invasive disease. Virulent strains are more likely to become invasive if there is an immune deficit, other concurrent respiratory infection such as influenza, or exposure to tobacco smoke. There is also higher risk in those living in poor, overcrowded conditions, with age peaks in infants and young adults. Most infections in Australia are from serogroups B and C, with C dropping markedly since the meningococcal C conjugate vaccine has been given routinely from age 12 months.

Health professionals are advised to treat meningococcal disease on suspicion, preferably after taking blood cultures and/or CSF. Nowadays, PCR testing can also be used to confirm cases if the organism is not able to be cultured from a clinical sample. A suspected case often generates confusion about the risk to relatives and health workers. Interestingly, cases are poor transmitters (i.e. spreaders) of meningococci, even before they receive antibiotics. Rather, most secondary cases seem to be infected by asymptomatic carriers in the patient's network of contacts. Risks of secondary disease in various types of contacts are estimated mainly from observational studies, because of the difficulties and ethical problems in performing trials. Even so, the risks to even the closest contacts are actually quite low and diminish toward the 'background' or population risk in casual contacts. Health workers are not at any significant risk unless they either gave mouth-to-mouth resuscitation or intubated a patient with meningococcal disease without wearing a mask.

Based on the best available evidence, only contacts that slept in the same household in the week before onset, and some 'household like' and sexual contacts are treated with antibiotics to clear them of possible meningococcal carriage.

It is estimated that about 200 people would be treated with clearance antibiotics to prevent one new case. Persons outside this defined group should not be treated because there are risks and immunological disadvantages in unnecessary antibiotic use. Close as well as distant contacts are given information about signs and symptoms of the disease because clearance antibiotics cannot always prevent further transmission and invasive disease. The very small but elevated risk of secondary cases relates mainly to the first week after contact – requiring a rapid public health response – but persists for at least a month (after which clearance antibiotic would not be justified).

Now a similar logic has led to the adoption of vaccination as well. Although the risk to even close household contacts is small, we have effective vaccines that induce protective responses two weeks after being given. Of these, the meningococcal C conjugate vaccine currently given to children at 12 months is the most effective and long lasting. A polysaccharide vaccine for groups A, C, W135 and Y only works well from age 2 years, and the protection is temporary.

The new (from 2008) approach in the national guideline is:

- Trace defined close contacts and offer clearance antibiotics and information. Offer opportunistic meningococcal C conjugate vaccine if this has been given previously to those born on or after 1 January 2002
- Await serogrouping of the meningococcal isolate or the PCR product
- If serogroup B, there is no appropriate vaccine available
- If a vaccine-preventable serogroup retrace only the 'close household' contacts
 - If serogroup C, immunise with the superior conjugate C vaccine (unless this has already been given)
 - If serogroup A, W135 or Y, immunise with the 4-valent polysaccharide vaccine if over two years of age.

Vaccination of close household contacts of invasive meningococcal disease will make a further but small contribution to preventing secondary cases. This new guideline makes prompt and careful tracing of those contacts even more important, and relies on the expert laboratory support we have available in Queensland.