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PEER REVIEWED FEATURE
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Whooping cough

optimising prevention

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Vaccination against pertussis should be encouraged on time as part of the schedule and for all adults that spend significant time with young infants.

Key points

- **Pertussis (whooping cough) is a highly infectious, vaccine-preventable disease.**
- **Action is required to protect infants who are too young to have received three doses of primary pertussis-containing vaccines.**
- **Vaccination against pertussis does not provide life-long immunity and it is recognised that patients are at risk of clinical pertussis five to 10 years after their last vaccination.**
- **Infants younger than 6 months of age with pertussis, or any other child with pertussis who is unwell, should be considered for hospital admission for supportive care to manage complications such as paroxysms, apnoea and feeding difficulties.**

Pertussis (whooping cough) is a highly infectious, vaccine-preventable disease. It causes significant morbidity and mortality in the developing and developed worlds, including Australia. Since late 2008, an Australia-wide pertussis epidemic has seen an increase in hospitalisations of infants with life-threatening pertussis. Action is required to protect infants who are too young to have received three doses of primary pertussis-containing vaccines. This article addresses diagnosis and management of patients with pertussis and outlines strategies to optimise prevention.

MICROBIOLOGY

Pertussis is caused by a Gram-negative bacillus *Bordetella pertussis* (Figure 1). It is highly infectious, spreading by respiratory droplet to up to 80% of susceptible household contacts.[1] Humans are the only known natural reservoir. *B. pertussis* secretes a number of toxins that contribute to the disease process. Pertussis toxins are involved in adherence to the tracheal wall damaging the epithelium. Systemic effects of the toxins include lymphocytosis and alteration of some hormonal activities, such as increased insulin production (resulting in hypoglycaemia) and increased sensitivity to histamine (resulting in increased capillary permeability, hypotension and shock).[2]

EPIDEMIOLOGY

Pertussis is endemic within Australia with a national epidemic occurring every three to four years. There is seasonal variation with most cases occurring in spring. Notifications of pertussis have increased in Australia over the past three years (Figure 2), especially among adolescents and adults. This is due, in part, to the increased awareness of the diagnosis in the community and the increased availability of

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diagnostic tests to GPs. However, this is likely to be a gross underestimation of the total cases as many adults (12 to 32%) with a persistent cough (more than 21 days) have unrecognised pertussis.[3]

Pertussis infections can be subclinical or asymptomatic. In Australia between 1993 and 2005 there were 18 deaths attributed to pertussis, 16 were among infants younger than 12 months of age.[1] There were a total of 8038 hospital bed days recorded with a diagnosis of pertussis between July 2002 and June 2005.[4] The pertussis hospitalisation rates in those younger than 3 months of age are higher in Indigenous compared with non-Indigenous infants.[5]

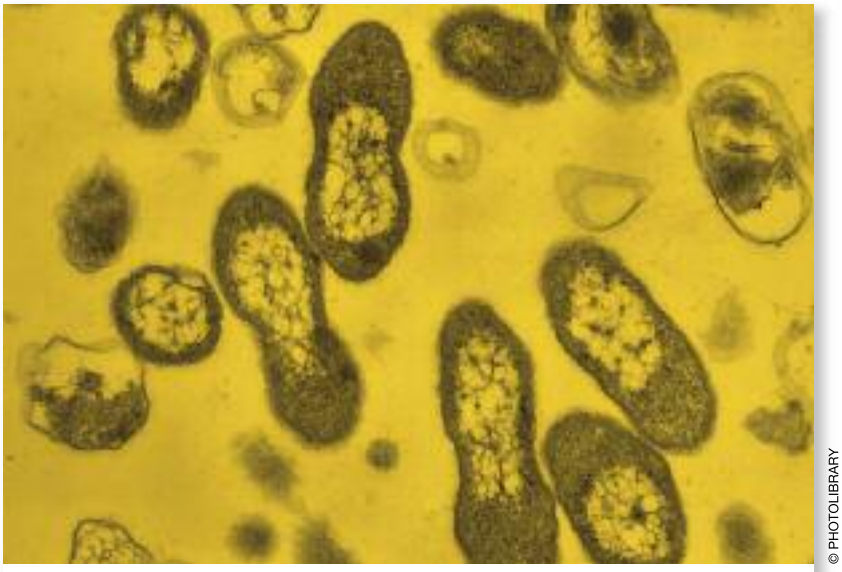

Figure 1. Transmission electron microscopy of *Bordetella pertussis* bacterium.

CLINICAL FEATURES

Pertussis has an incubation period of 14 days (range from seven to 20 days). Initial symptoms resemble an upper respiratory tract infection (coryzal phase), lasting one to two weeks. This is followed by the paroxysmal cough (paroxysmal phase), lasting four to six weeks. Symptoms improve over subsequent weeks to months (convalescent phase).

The classic inspiratory whoop occurs at the end of a prolonged run of coughs and is more common in infants. Older children and adults rarely whoop although many experience posttussive vomiting. Apnoea may be the first clinical sign in infants. There is often little or no fever. Infants with pertussis often look well between coughing paroxysms with no clinical signs on auscultation of the chest. A patient is infectious just prior to the onset of cough, and if untreated for up to 21 days after the onset of cough. The clinical course stays true to its historical name, the '100-day cough', with prolonged sleep disturbance and weight loss common in all ages.

A modified illness can occur in individuals with waning immunity. Vaccination against pertussis does not provide life-long immunity and it is recognised that patients are at risk of clinical pertussis five to 10 years after the last vaccination. An increasing number of fully vaccinated children and adolescents with pertussis are being identified in the current epidemic. There may be many factors contributing to this, including shorter protection offered by the acellular pertussis vaccine compared with the whole-cell vaccine.[6] Even natural infection does not provide life-long immunity, although the duration of protection

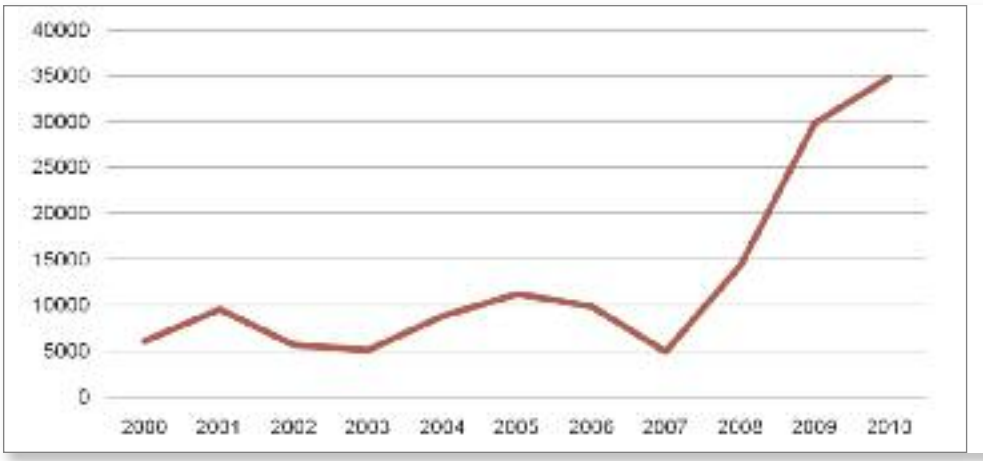

Figure 2. Total number of notifications of pertussis per year.*

* Data from the Australian Department of Health and Ageing, National Notifiable Diseases Surveillance System [online]. Accessed May 2011. Available from www9.health.gov.au/cda/Source/CDA-index.cfm

CASE DEFINITIONS FOR PERTUSSIS

National case definition (from January 2004)[4]

Definitive laboratory evidence

- Isolation of *Bordetella pertussis* from a clinical specimen or detection of *B. pertussis* on polymerase chain reaction

or

Laboratory suggestive evidence (and clinical evidence)

- Seroconversion or significant increase in antibody levels or fourfold or greater rise in titre to *B. pertussis*, in absence of recent immunisation, or
- Single high immunoglobulin A titre to whole cells, or
- Detection of *B. pertussis* antigen by immunofluorescence assay

or

Clinical evidence (and an established epidemiological link to confirmed case)

- Coughing illness lasting two or more weeks, and
- Paroxysms of coughing, inspiratory whoop or post-tussive vomiting

Probable case definition

Clinical evidence only

All suspected or confirmed cases of pertussis should be notified to the state or territory public health authorities.

A SUMMARY OF THE DIAGNOSTIC TESTS FOR PERTUSSIS[2,6,7]

Culture

- Gold standard diagnostic test
- Highly specific
- Sensitivity of 0 to 67% even if coughing for less than three weeks
- Can take up to one week to become positive
- Best sample with respect to sensitivity is nasopharyngeal aspirate, followed by pernasal swab and throat culture
- Dacron or calcium alginate swab should be used because cotton and rayon swabs are inhibitory
- Decreased sensitivity with longer duration of illness (0% at >three weeks)
- Decreased sensitivity in older patients, those who are vaccinated or those receiving antibiotics
- 30% increase in positive culture rate if the swab is put straight into culture medium

Polymerase chain reaction (PCR)

- Sensitivity of 73 to 100% (much higher than culture)
- Specificity of approximately 100%
- Dacron or rayon swabs can be used for PCR sample collection, not calcium alginate
- Can be performed on throat swabs
- Decreased positivity with increased duration of illness (can be positive up to six weeks after onset of symptoms)
- Less affected by antibiotic use than culture

Serology

- Positive serology may occur only after six weeks of being unwell
- Measurement of antipertussis toxin antibodies are used, immunoglobulin (Ig) A and IgG
- IgA is most commonly used in Australia with a sensitivity of a single IgA of 24 to 62%
- Positive pertussis IgA is highly specific in a setting of clinically compatible illness
- Twofold increase or more in titres between acute and convalescent samples are diagnostic
- IgA is specific for infection rather than immunisation, whereas a raised IgG titre can occur with either
- There is anecdotal evidence that IgA is less reliable in infants and can persist indefinitely after an infection
- Single IgG has a good predictive value for acute infection, sensitivity of 76% and specificity of 99% in immunological-naïve patients
- Combining IgA and IgG improves sensitivity but is expensive for routine diagnostic use

Others

- Direct fluorescent antibody testing is not available in Australia due to problems with sensitivity and specificity

is longer than after vaccination.

Patients with a modified illness may have only a persistent cough so that the diagnosis is frequently missed. All cases of modified illness are infectious so pose a risk to unprotected infants.

COMPLICATIONS

Pertussis pneumonia is a diffuse process, can develop rapidly and can be fatal. Coughing can cause hypoxia, subconjunctival haemorrhage and intracranial haemorrhage as well as disturbed sleep and feeding patterns (leading to weight loss). Electrolyte disturbances or hypoxia can cause seizures and encephalopathy. Significant morbidity and mortality is highest among infants younger than 6 months of age.

MAKING THE DIAGNOSIS

Diagnosis is often based on clinical features. Laboratory tests can be used to aid with diagnosis but are not essential (see the box on this page).[4] A summary of

RECOMMENDED ANTIBIOTICS FOR TREATMENT AND PROPHYLAXIS* OF PERTUSSIS[1]

Azithromycin†

- Child (<6 months of age) 10 mg/kg/dose daily for five days
- Child (>6 months of age) 10 mg/kg/dose (max 500 mg) on day one, then 5 mg/kg daily on days two to five
- Adult 500 mg single dose day one, then 250 mg daily on days two to five

Clarithromycin

- Child (>1 month of age) 7.5 mg/kg/dose (max 500 mg) twice daily for seven days
- Adult 500 mg twice daily for seven days

Erythromycin

- Child (>1 month of age) 10 mg/kg/dose (max 250 mg) four times daily for seven days
- Adult 250 mg four times daily for seven days

Cotrimoxazole (trimethoprim/sulfamethoxazole; if macrolide antibiotics cannot be used)

- Child (>2 months of age) 4 mg/kg/dose (trimethoprim component, max 160 mg) twice daily for seven days
- Adult 160/800 mg twice daily for seven days

* Drug and dosing recommendations for prophylaxis are the same as that for treatment.

† Azithromycin is the recommended antibiotic for infants younger than 1 month of age, in view of the risk of pyloric stenosis associated with the use of erythromycin.

Note: roxithromycin has not been proven to be effective against *Bordetella pertussis* and should not be used.

diagnostic tests with important sample information (positive and negative) is shown in the box on page 42.[2,6,7] In general, culture and polymerase chain reaction are recommended if samples can be obtained early in the illness, otherwise serology testing should be considered.

MANAGEMENT AND TREATMENT

Index case

Infants younger than 12 months of age with suspected pertussis need urgent assessment. The lack of physical signs between coughing paroxysms should not prevent careful monitoring for complications. Episodes of apnoea and cyanosis are life-threatening. Infants with pertussis who are younger than 6 months of age, or any other child with pertussis who is unwell, should be considered for hospital admission for supportive care to manage complications such as paroxysms, apnoea and feeding difficulties. Management of patients with paroxysms is limited to the provision of oxygen, either during the paroxysm or continuously, to ensure oxygenation is maintained when the infant coughs. Intensive care support may be required. Children, adolescents and adults with pertussis rarely need hospitalisation.

Antibiotics may alter the disease course if given within the coryzal or early paroxysmal phase; however, the diagnosis is not usually known at this early stage. In most cases of pertussis, antibiotic treatment is to prevent the spread of infection. Suggested antibiotic therapy is presented in the box on this page.[1] Although macrolides form the cornerstone of therapy, roxithromycin has not been proven to be effective and should not be used.[8] Multiple treatments have been tried to alleviate the cough, but none are beneficial.[9]

Patients should be excluded from childcare, school or work until they have received at least five days of antibiotics or are three weeks after the onset of the paroxysmal phase. A family and contact history should be sought to identify at-risk infants, incompletely immunised children, and adolescents and adults who have not received a pertussis booster in the past five years. If unimmunised or partially immunised children are diagnosed with pertussis, they should still complete the pertussis immunisation schedule.

PRINCIPLES OF PERTUSSIS CONTACT MANAGEMENT

- Pertussis is highly infectious
- Adults are the main source of infection for infants
- Immunity to pertussis following vaccination protects against life-threatening complications but may not completely protect against infection that can be spread
- Immunity from vaccination is not life long and wanes after five years
- Infants younger than 24 months who have not had three doses of pertussis-containing vaccine are most vulnerable to infection and life-threatening complications of pertussis
- Side effects of macrolide antibiotics are low (especially azithromycin and clarithromycin)
- Side effects of booster doses of a pertussis-containing vaccine are low

Contacts of cases

Antibiotics

The evidence in the literature for antibiotic treatment of pertussis contacts is limited. The only two studies addressing this issue are poorly performed and do not distinguish between contacts who were immunised or not. Therefore, recommendations for contact prophylaxis are based on expert opinion; however, the recommendations are complex because of the many clinical variables.

In our experience this often leads to undertreatment of contacts and, in light of the current epidemic, thorough management of contacts is required. The initial step is a detailed history of possible contacts and their vaccination histories. The principles of contact management are presented in the box on this page.

Prophylaxis with antibiotics is recommended for high-risk contacts of pertussis cases to protect young infants who are at

risk of life-threatening pertussis.[1] These high-risk contacts include:

- household contacts when the household includes any child younger than 24 months who has received fewer than three doses of pertussis-containing vaccine
- women in the last month of pregnancy, regardless of immunisation status
- children or adults within a childcare setting, regardless of immunisation status, where the index case attended for more than one hour while infectious, and that the childcare setting includes any child younger than 24 months who has received fewer than three doses of pertussis-containing vaccine
- healthcare staff, regardless of vaccination status, working in a maternity unit or newborn nursery
- all babies within a maternity unit or newborn nursery where a case attended for more than one hour while infectious.

It is our practice, during this current epidemic, to have a broader consideration for antibiotic treatment of household contacts. We favour giving antibiotics to all household contacts of cases to reduce the chance of clinical disease and reduce the spread of pertussis in the community. This differs from the immunisation handbook whose recommendations are focused on the high-risk settings outlined above.[1]

Vaccination

Children up to 8 years of age who are household contacts should be given a dose of DTPa-IPV (combined diphtheria, tetanus and pertussis [acellular] and inactivated poliovirus [quadrivalent]) as soon as possible if they are only partially vaccinated. Older close contacts should receive a dose of dTpa (diphtheria, tetanus and pertussis [acellular]) if they have not had a pertussis-containing vaccine in the past five years.

PREVENTION STRATEGIES

Educate and inform

The public and healthcare providers need to be informed about the current pertussis epidemic and strategies to optimise protection from the disease.

Protect infants from pertussis

The highest priority is the protection against pertussis in infants younger than 12 months of age. Vaccinating parents of new babies is recommended throughout Australia, although only funded in some states. Ideally, both parents should receive the vaccine prior to the woman becoming pregnant. Alternatively, expectant fathers (or partners) should receive their dose during the pregnancy, and the mothers vaccinated as soon as possible after delivery. Healthcare providers should consider vaccinating all other close family members (grandparents and carers) and siblings if more than five years since their last pertussis-containing vaccine.

Immunise on time

Healthcare providers should improve the timeliness of the primary schedule and booster pertussis vaccines.

Increase immunisation coverage

Healthcare providers should improve the coverage of pertussis immunisation at all ages by giving an infant three doses of a pertussis-containing vaccine and then a preschool booster and adolescent booster dose. The percentage of Indigenous and non-Indigenous Australian children fully immunised at 30 June 2010 are shown in the Table. For adults we recommend 'cocoon vaccination', which means all people who have contact with infants younger than 6 months of age, such as childcare workers or new parents and grandparents, should receive a booster dose.

IMMUNISATION

Vaccines

Acellular pertussis-containing vaccines replaced whole-cell pertussis vaccines for both primary and booster doses in Australia in 1999. The DTpa fourth dose, at 18 months of age, was ceased in 2003. The adolescent school program replaced ADT (adult diphtheria and tetanus) with dTpa in 2004. The acellular pertussis-containing vaccines have three or more purified components of *B. pertussis*. The range of side effects is the same with the acellular pertussis-containing vaccines compared with the whole-cell vaccines; however, the rates of the potential side effects are dramatically reduced with the acellular vaccines.[1] Significant potential adverse events such as a hypotonic-hyporesponsive episode can still occur in infants receiving the acellular vaccine but they are much less common.

Timing

The pertussis-containing vaccine is given as a combination vaccine in the primary course. This course should be given at 2, 4 and 6 months of age, but can be started at 6 weeks of age. It is safe to do so and is now a World Health Organization recommendation although only some states in Australia have adopted this policy to date.[10] If the course is interrupted, it should be resumed and not repeated. An infant receiving the first dose late can receive the next doses at four-week intervals to catch up. When the 18-month booster was ceased, the preschool booster was brought forward to the fourth birthday rather than the 4 to 6 year age range. In the face of the current pertussis epidemic, some states are recommending the preschool booster be given from 3.5 years of age.

The adolescent pertussis-containing booster was introduced at different ages around Australia. Western Australia commenced at year 7 (12 to 13 year olds) with a catch-up program for years 7 to 12 (12 to 18 year olds). In Victoria, the adolescent

TABLE. Immunisation coverage for pertussis*

Age (months)	Non-Indigenous children (%)	Indigenous children (%)
12 to <15	91.5	84.5
24 to <27	92.4	90.7
60 to <63	89.9	85.7

* Data from Communicable Disease Prevention and Control, Department of Health Victoria, Australian Childhood Immunisation Register. Immunisation coverage rates calculated at 30 June 2010.

dose is given in year 10 (15 to 16 year olds) but with no catch-up program. This timing was decided with the hope of having residual immunity by the time that cohort were becoming parents.

The future

A neonatal dose of pertussis-containing vaccine is being further investigated but the trials are limited so far. There has been a trial that has shown that giving two doses of acellular vaccine at birth and at 1 month of age induces an antibody response that may protect young infants against pertussis. This looks promising but needs further evaluation.[11] Timing of the adolescent booster varies between states and territories. There is potential to consider those with a year 10 booster bringing this forward to year 7 with a catch-up program.

Adult vaccination needs to be encouraged when planning a pregnancy. The current pertussis-containing adult vaccines are recommended for single booster dose use. We should review the need and timing of repeat booster doses to ensure adults with waning pertussis vaccine immunity do not expose infants less than 6 months of age to pertussis.

The immunisation coverage inequality among Indigenous Australians needs to be addressed. Another issue currently under investigation is that of genomic adaptation of *B. pertussis*.[12] The use of acellular vaccines may have driven antigenic changes of two clones that are now predominant in Australia.

CONCLUSION

In summary, there are still a number of questions that need to be answered to understand the disease and the actions of the vaccines better. In the meantime we must encourage vaccination against pertussis as part of the schedule and in adults who spend significant time with young infants. MT

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