# Pertussis in Australia today

## A disease of adolescents and adults that can kill infants

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**BACKGROUND**
Adolescents and adults are the main reservoir of pertussis infection in Australia today. Diagnosis in these age groups can be difficult because of atypical clinical presentations and limitations of laboratory investigations.

**OBJECTIVE**
This article discusses the common presentation of pertussis in adults and adolescents, the use and limitations of laboratory testing, and appropriate treatment and prophylaxis.

**DISCUSSION**
The reason for treating cases and providing chemoprophylaxis for contacts is to prevent infection in infants, who account for 90% of deaths from pertussis. Treatment with the newer macrolides appears to be as effective as erythromycin and with less side effects; however, roxithromycin should not be used as its in vivo efficacy is unproven. The majority of pertussis cases will be seen in general practice – most likely during the infectious period – therefore general practitioners need to consider being vaccinated with dTpa against pertussis.

**Pertussis ('whooping cough') is a respiratory illness due to *Bordetella pertussis*, a gram negative bacterium. Some milder cases of pertussis are caused by *B. parapertussis*. It is transmitted by droplet infection and has approximately an 80% attack rate for susceptible contacts.[1]**

## Changing epidemiology of reported pertussis

The World Health Organisation reported that 17.6 million cases of pertussis occurred globally in 2003; 90% from developing countries.[2] However, developed nations have notification rates for pertussis that are not insignificant (about 40/100 000 per year in Australia and 10–35/100 000 per year in Canada[3,4]). In the United States, pertussis is the only disease with recommended universal childhood vaccination which has had an increase in reported cases.[1,5] Despite the increase in reported cases of pertussis, these are still likely to be underestimates.

Pertussis immunisation programs have been in place for 50–60 years in many developed nations. Data from the USA from the pre-vaccine era show that only 7% of recognised cases of pertussis occurred in patients over 10 years of age; however from 1997–2000 this number rose to 50%.[6] In Australia, this phenomenon has also occurred, with 90% of pertussis notifications from 2003–2005 in individuals over 10 years of age (22545/25048 notifications).[3] The possible reasons for this shift in the epidemiology of reported pertussis include:

- improved diagnostic tests
- increased awareness among the medical community of pertussis in the older age group, and
- waning immunity in adolescents and adults from childhood immunisation and/or prior infection.

Although only 10% of notifications for pertussis occur in individuals less than 10 years of age, it is this age group, in particular infants less than 6 months of age, who suffer the most severe infections and highest mortality. In Australia from 1993–2002, there have been 16 deaths attributed to pertussis, of which 15 (94%) occurred in infants under 12 months of age.[7] USA data have shown that 90% of deaths attributable to pertussis occurred in infants less than 6 months of age.[8] Therefore, failure to recognise pertussis in adolescents or adults in a timely fashion could result in transmission to young children, with dire consequences.

There is one aspect of the epidemiology of pertussis which, unfortunately, hasn't changed between the pre- and post-vaccine eras: a cycle of endemic pertussis is still interrupted by an epidemic every 4 years or so. Other vaccine preventable diseases such as measles continue to have epidemic cycles, but the time interval between epidemics has increased since the introduction of immunisation programs. This suggests

that pertussis is circulating in a similar fashion nowadays to the pre-vaccine era, except that the main reservoir is now adolescents and adults.[6]

## Clinical features

Adolescents and adults often don't present with the classic pertussis syndrome seen in young children. However, it is worth discussing these features to highlight the consequences of a child being infected by an adult or adolescent.

### Classic pertussis

After an incubation period of 7–10 days (5–21 days) the illness begins and consists of three phases: catarrhal, paroxysmal and convalescent.[1,8] During the catarrhal phase (7–10 days), the patient complains of a runny nose, runny eyes and a mild cough. It is the next phase, the paroxysmal phase, which is well recognised.

The paroxysmal phase lasts 2–8 weeks and is characterised by fits of coughing throughout the day and night (often worse at night). Typically 5–10 powerful coughs will occur in one expiration followed by a deep and noisy inspiration – this inspiratory breath gives rise to the 'whoop' of whooping cough. To an observer (particularly a parent), the paroxysm can be a terrifying spectacle – the individual may become cyanosed, have bulging of neck veins and eyes, protrusion of the tongue, profuse salivation, and lacrimation. The paroxysm may be followed by vomiting. Although the individual may be normal between paroxysms, children in particular are prone to weight loss and are often subdued.

Complications of pertussis can be divided into those attributable to the pressure effects of the paroxysmal coughing or to those not due to the pressure effects. The intrathoracic and intraabdominal pressures generated by the paroxysms are enormous and can result in the following complications: carotid artery dissection, intracranial haemorrhage, cough syncope, fractured ribs, subconjunctival haemorrhage, incontinence, hernias, ruptured vertebral discs, ruptured diaphragms, epistaxis, melaena, ulcerated frenulum, rectal prolapse, pneumothoraces and severe alkalosis with seizures.[8,9] Complications in pertussis not attributable to pressure effects occur in about 5% of individuals, most commonly neurological and respiratory. The respiratory complications include pneumonia and otitis media (due to pertussis itself or to secondary infection); neurological complications include encephalopathy and seizures. The incidence of encephalopathy is about 0.9 per 100 000 cases.[2] The proportion of complications (as with mortality) is highest in infants less than 6 months of age.

The convalescent phase lasts 1–2 weeks and occurs with a gradual reduction in the frequency and severity of symptoms. During this stage, an intercurrent viral respiratory tract infection can precipitate further paroxysms but these are not due to pertussis.

### Pertussis in adolescents and adults

Partially immunised adolescents and adults, as well as previously immunised children, can present with an atypical illness. This may be a chronic cough without the whoop or post-tussive vomiting. The proportion of whooping among adults varies with studies showing 8–82%.[10] Post-tussive vomiting of classic pertussis occurs in 17–50% of adult cases.[5] Another issue, which has obvious implications for surveillance, is that asymptomatic infection can occur. A randomised controlled trial examining the efficacy of the acellular vaccine found that seroconversion to pertussis among asymptomatic participants was 5–10 times more common than among symptomatic individuals.[11] Therefore, atypical presentations of pertussis present both diagnostic difficulties for clinicians and surveillance difficulties for health departments.

If pertussis presents simply as chronic cough illness in this age group, conversely one may ask what proportion of chronic cough illnesses are due to pertussis? This question has been addressed by a number of studies with varying results (5.7–52.0%). During nonepidemic periods, this proportion attributable can be as low as 1% (range 1–17%).[6,11] Part of the reason for the variable findings in studies includes whether or not the study was conducted during an epidemic cycle, differing levels of awareness among doctors of pertussis, and differences in diagnostic tools. Certainly, it appears that pertussis is an important cause of chronic cough but is only one among many causes.

## Differential diagnosis of a chronic cough illness

Apart from *B. pertussis*, other infective causes of a chronic cough include other Bordetella species, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, adenovirus, and other respiratory viruses.[8] Common noninfective causes include postnasal drip, gastrooesophageal reflux disease, and medications such as angiotensin converting enzyme inhibitors.

## Diagnostic tests

Laboratory diagnosis of pertussis, irrespective of the technique used, is not a very sensitive tool. This lack of sensitivity has been taken into account with the national case definition for pertussis, where probable cases (ie. those with only clinical features of pertussis and negative laboratory results) have to be notified in addition to confirmed cases.[12] The take home message for clinicians and epidemiologists alike is that a positive result is useful but a negative result doesn't exclude pertussis in their patient. In addition, the type of swabs (eg. Dacron, cotton, calcium alginate) and correct anatomical site for swab collection differs for polymerase chain reaction (PCR) and culture, further adding to confusion for clinicians. Tests include:

- culture
- PCR, and
- serology.

Direct fluorescent antibody testing of nasopharyngeal specimens isn't widely used in Australia due to problems with sensitivity and specificity.

### Cultures

Culture of pertussis from nasopharyngeal specimens has been regarded as the 'gold standard' for laboratory diagnosis; unfortunately, it is an insensitive test. Sensitivities of culture have been estimated as low as 0–67%.[13,14] The consequences of this poor sensitivity have not only been to limit the use of culture in the diagnosis of pertussis, but also to generate uncertainty about the specificity of the other diagnostic tests for pertussis. This is because a gold standard should be the reference against which other tests should be judged.

Regan-Lowe medium is widely used for culturing pertussis. It consists of cephalexin (to

inhibit the growth of oropharyngeal flora), charcoal (to absorb toxins) and horse blood (to promote growth of *B. pertussis*). The original culture medium developed by Bordet and Gengou in the early 1900s is also still popular; however, the Regan-Lowe medium has the advantage over Bordet-Gengou of being able to be stored in the refrigerator for 1 month.[14] Cultures can be positive after 3 days, but often take 1 week to become positive. Timing of cultures is important as they will only be positive 2–4 weeks after the onset of the catarrhal phase (or 1–3 weeks after the onset of the paroxysmal phase, or a few days after starting antibiotics).[15]

Clinicians need to remember that specimens for culture should only be taken from the nasopharynx as *B. pertussis* is found in areas with ciliated epithelium. Therefore, specimens from the anterior nose, throat and sputum are of little value. The sensitivity of the culture will be increased if the specimen is a nasopharyngeal aspirate rather than a swab (many general practitioners will not be able to perform an aspirate in their rooms). There is almost a 30% increase in yield of positive cultures if the specimen is immediately inoculated into culture medium at the bedside, which again will be logistically difficult for many GPs.[16]

It is unfortunate that there are so many difficulties with culture of pertussis as a positive result is almost 100% specific for infection. It can also discriminate between *B. pertussis* and *B. parapertussis* as causes of pertussis.

### Polymerase chain reaction

Polymerase chain reaction has a number of advantages over culture:

- unlike culture specimens, PCR can be performed on throat swabs
- PCR has a higher sensitivity than culture, increasing the rate of identification of pertussis from 2.6–4.0 times[17,18]
- PCR will not be as readily affected by prior antibiotic therapy, and
- PCR tests will remain positive for longer than cultures – up to 6 weeks after the onset of symptoms[19]
- however, the sensitivity of PCR will decrease with time.

Like cultures, PCR can differentiate *B. pertussis* from *B. parapertussis* (depending on the primers used). The main disadvantage is that false positives can occasionally occur.[8]

### Swabs for PCR and culture

In broad terms, there are three types of swabs commonly used to isolate bacteria: cotton, calcium alginate and Dacron. For culture of pertussis, cotton swabs can't be used, while for PCR, only Dacron swabs can. The difficulties in remembering this information is added to by the fact that many swab packets don't specify whether the swab is cotton, calcium alginate or Dacron.

### Serology

The most commonly used serological assay for diagnosing pertussis is an enzyme linked immunosorbent assay (ELISA). The type and number of pertussis antigens will vary between assays. Antigens used include adhesins such as pertussis toxin (PT), pertactin (PRN), filamentous haemagglutinin (FHA) and fimbriae. Although only PT is specific for *B. pertussis* (the others are also expressed by other Bordetella species), a rise in FHA correlates with acute *B. pertussis* infection.[20]

Only IgG and IgA are used to make a diagnosis of pertussis. The diagnosis can be made on a single high titre or a greater than two fold rise between baseline and convalescent titres.[8] Interestingly, there are data demonstrating that a fall in IgG titre against pertussis toxin and filamentous haemagglutinin can also represent acute infection.[21] IgA is specific for infection rather than immunisation, however, a raised IgG titre can occur with either. Despite this, a single IgG titre against PT above 100–125 EU/mL is consistent with acute infection.[19] In Australia, IgA seems to be the most common antibody test used.

As with PCR and culture, serology has its limitations. The sensitivity of a single IgA titre may be low with one study estimating 24–62%.[20] Even specificity can be a problem due to cross reactivity with other Bordetella species. Also, a positive serology result may not appear until the patient has been unwell for 6 weeks. The IgA test is not very reliable in infants. Anecdotal reports suggest that IgA can persist indefinitely after an infection. But despite these limitations, a positive pertussis IgA will be highly specific in the setting of a clinically compatible illness.

### Full blood count

Lymphocytosis with a lesser degree of neutrophilia is the classic finding in pertussis. This is due to the action of PT. In fact, there may be an association with the level of lymphocytosis in children with pertussis and death.[22] However, adults and other partially immunised groups may have a normal white cell count and differential.[8]

Based on the above information, *Table 1* shows an approach to making a diagnosis of pertussis using a combination of investigations during different times of the infection.

## Treatment and chemoprophylaxis

For the clinician seeing a patient with suspected pertussis, the issues that need to be addressed during the consultation (apart from investigations) are:

- notification to the health department or public health unit
- whether the patient is within the window period to receive treatment
- which antimicrobial agent to use.

All clinically suspected pertussis cases must be notified to the health department or public health unit. The clinician should do this as soon as possible, ideally during the consultation, in order for public health officials to assist in the identification of susceptible contacts and promptly initiate postexposure chemoprophylaxis.

*B. pertussis* is spontaneously cleared from the nasopharynx of adults by 3 weeks after the onset of the cough and up to 6 weeks after the onset of the cough in infants.[1] This is the basis for determining if the patient should receive treatment or not. There is a slight difference in recommendations from different countries about the correct timing of treatment. In Australia and the United Kingdom, the recommendation is to commence treatment within 21 days of the onset of symptoms.[23,24]

If the patient is within the window of opportunity to commence treatment, a macrolide antibiotic is the treatment of choice. It should be made clear to the patient that antibiotic therapy will render them noninfectious but will be unlikely to alter the course of their illness.[25] The patient will only become noninfectious after 5 days of antibiotic therapy and may therefore need to be excluded from work for this period. The dose and duration of antibiotics is similar for both treatment

**Table 1. Using a combination of PCR and serology to make a laboratory diagnosis of pertussis**

| Weeks after onset of symptoms | PCR* | Baseline serology** | Convalescent serology 2–4 weeks later | Single serology adequate |
|---|---|---|---|---|
| <2 weeks | Yes | Yes | Yes | No |
| 2–6 weeks | Yes | Yes | Yes | Maybe |
| >6 weeks | No | No | No | Yes |

* If PCR is not available, nasopharyngeal cultures can be taken in the first 2–4 weeks after the onset of symptoms

** Serology is not reliable in children under 2 years of age

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of pertussis and chemoprophylaxis of contacts. Erythromycin has been the mainstay of pertussis treatment for many years. However, studies have found that the newer macrolides – clarithromycin and azithromycin – are equally effective as erythromycin in eradicating *B. pertussis* with the added benefit of fewer side effects than erythromycin and better compliance.[26,27] Australian guidelines recommend the use of clarithromycin or azithromycin (in addition to erythromycin) for treatment and postexposure prophylaxis of pertussis.[28] A Cochrane review on the role of antibiotics in treating pertussis concluded that both clarithromycin and azithromycin are effective antibiotics.[25] Unfortunately in Australia, azithromycin is only approved for use in pertussis under the Repatriation Pharmaceutical Benefits Scheme and not the Pharmaceutical Benefits Scheme.[29] For patients allergic to the macrolides, cotrimoxazole (trimethoprim-sulfamethoxazole) can be used instead.

A number of antibiotics have shown in vitro efficacy against *B. pertussis* but have unknown clinical efficacy.[1,30,31] For Australian clinicians, the most important of these is roxithromycin, a widely used macrolide.[32] The take home message is that roxithromycin should not be used for treatment or chemoprophylaxis of pertussis until further studies demonstrate its clinical efficacy in this setting.

## Treatment of neonates

For neonates receiving erythromycin there is an increased risk of infantile hypertrophic pyloric stenosis (IHPS).[33,34] The USA has addressed this by recommending azithromycin as the preferred antimicrobial agent for neonates, as it has not been associated with IHPS to date. If azithromycin is not available, then erythromycin should be given as the risk of neonates having a life threatening course of pertussis outweighs the risk of IHPS from erythromycin.[1] Parents of neonates receiving erythromycin should be made aware of this issue. There are conflicting data about whether neonates breastfeeding from mothers on erythromycin are also at increased risk of IHPS (the use of azithromycin in breastfeeding mothers of neonates may be a possible solution to this).[35,36]

## Treatment of pregnant women

Unlike many infections, maternal antibodies do not guarantee protection of the neonate against developing pertussis. Therefore, it is recommended that women in the last trimester of pregnancy who have been exposed to pertussis should receive chemoprophylaxis.[24] Cotrimoxazole and the three macrolides discussed each have a different safety category for use in pregnancy.[37] Erythromycin (Category A) is the safest antibiotic to use in pregnancy for pertussis and is the recommended agent by the National Health and Medical Research Council.[24] Azithromycin is probably safe as well (Category B1). Clarithromycin (Category B3) and cotrimoxazole (Category C) for pertussis should be avoided in pregnancy if erythromycin can be safely given. Ideally, parents should be immunised with a booster dose of dTpa before planning a pregnancy or soon after birth (ideally before the neonate is discharged from hospital).[24]

## Immunisation and GPs

The role of immunisation in preventing pertussis in children and high risk adults (eg. maternity and nursery staff) is a topic beyond the scope of this article. However, as adolescents and adults with waning immunity are the main reservoir of pertussis in the community, and as these groups tend to have only a mild illness, it follows that GPs will see the majority of them. It is also likely that a consultation with these patients will take place within the infectious period (ie. within 3 weeks of the onset of cough). In addition, it is recognised that a medical examination of the mouth, nose and throat[1] and face-to-face exposure[38] with a patient are risk factors for contacts developing pertussis; therefore, doesn't it follow that GPs need to be immunised against pertussis? The consequences of GPs developing pertussis not only have infectious implications for their own families, but also for their patients, especially infants. Which GPs (or adults in general) are likely to be susceptible to pertussis? Although the figures differ between studies, it is thought that infection with pertussis and immunisation against pertussis provide around 15 years and 6–12 years of immunity respectively.[2,13]

The only vaccine recommended for adult use in Australia is dTpa (Boostrix). Like childhood DTPa vaccine, dTpa contains diphtheria, tetanus and acellular pertussis constituents, but in lower amounts than those found in the childhood vaccine. dTpa costs approximately $40. The main concern of booster immunisation among adults is fear of local reactions to the tetanus component of the vaccine (there is no stand alone pertussis vaccine available). However, a recent study in Canada showed that it was safe to give dTpa as soon as 18 months after a previous immunisation with tetanus toxoid (eg. TD or Td39). Also, adults who have recently had a pertussis infection can safely be vaccinated.[24]

## Conclusion

General practitioners are likely to encounter more pertussis than other health care workers, therefore they need to familiarise themselves with its clinical presentations in adolescents and

adults and understand the use and limitations of laboratory tests in making a diagnosis. There is a strong argument for GPs to be vaccinated against pertussis with dTpa.

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