thebmj

BMJ 2019;364:l401 doi: 10.1136/bmj.l401 (Published 22 February 2019)

PRACTICE

CLINICAL UPDATES

Pertussis (whooping cough)

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What you need to know

- Suspect pertussis in patients with 2 weeks of cough and coughing paroxysms, post-tussive vomiting, inspiratory whooping, no fever, or exposure to a person with confirmed pertussis
- Immunisation is no guarantee of protection as vaccine efficacy decreases with time
- Antibiotics within the first 21 days of illness can prevent transmission, but cough is likely to last up to three months and there are no recommended treatments for it
- Consider admission if patient is clinically unwell or less than 6 months old, when mortality is higher
- Report suspected and confirmed cases of pertussis to local public health agencies to initiate infection control measures
- Offer pertussis vaccination to pregnant women in the second or third trimesters of pregnancy as it can provide passive immunity to neonates and young infants

Pertussis, also known as whooping cough, is caused by the Gram negative bacterium *Bordetella pertussis*.[1] It is transmitted via airborne droplets and is highly infectious.[2] Diagnosis is often delayed or missed,[3] as pertussis mimics the presentation of a viral upper respiratory tract infection and can sometimes present atypically.[2] In this article, we review the management of pertussis and present recent evidence and guidance on prevention through vaccination.

Sources and selection criteria

We performed a Medline search from January 2007 to December 2018 using the search terms 'whooping cough' and 'pertussis.' We included journal papers that we encountered from references of the papers from the initial search. We performed a similar search in the Cochrane database. We consulted the Public Health England website and the Centers for Disease Control and Prevention for guidelines on pertussis. We have referred to recent systematic reviews, meta-analyses and literature reviews in writing this manuscript but have cited individual clinical studies where there is no higher quality of evidence.

How common is it?

Pertussis affects nearly 24 million children under the age of 5 years each year and causes 160 000 deaths in this age group.[4 5] Peak incidence is seen in infants up to 6 months of age.[6] This may be due to the timing of vaccination in the latter part of or after this six month period. In the UK and Australia, which have an accelerated primary vaccination schedule at 2, 3, and 4 months, higher incidence and hospitalisation rate is observed in those under 3 months old compared with older infants.[7] Mortality is high in this group,[1 8 9] possibly due to an immature immune system and incomplete primary immunisation.[10]

About 3% of adults presenting with acute cough in European primary care have pertussis.[3] Outbreaks of pertussis have been reported periodically every two to five years, mainly in adolescents and adults.[11] Overweight or obese people and those with pre-existing respiratory conditions such as chronic obstructive pulmonary disease (COPD) or asthma are at increased risk.[12-14]

How do patients present?

After an incubation period of 4-21 days from exposure, patients present with symptoms of an upper respiratory tract infection such as coryza, low grade fever, and cough.[5 15] This is followed by the classic signs of pertussis: cough paroxysms followed by characteristic inspiratory whoop and vomiting[15] that can last for up to 10 weeks, followed by recovery. Coughing may be mild or severe. The illness can last up to three months and is colloquially termed "the 100 day cough."[16] Figure 1 presents the typical course of pertussis.

Occasionally patients present with atypical symptoms[2 18 19] such as breathlessness, wheeze,[20] fever, flushing, and stridor in children, and diarrhoea and breastfeeding difficulties in infants.[21] Adults may report sneezing attacks, sweating, hoarseness of voice, headache, sleep disturbance, weight loss, and fatigue.[22 23]

How is it diagnosed?

Making a clinical diagnosis is often difficult due to overlapping symptoms with an upper respiratory tract infection. Patients are

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often diagnosed after the 21 day window when antibiotics may be useful to prevent transmission. Pertussis may not be suspected in patients who have completed their vaccination schedule under the assumption that vaccination confers lifelong immunity.

Suspect pertussis in patients with characteristic features, listed in box 1. Presence of symptoms for two weeks is helpful but not essential to make a diagnosis.[27 28] The presence of post-tussive vomiting and inspiratory whoop in adults increases the likelihood of pertussis (sensitivity 30-33%, specificity 78%-80%) according to a systematic review and meta-analysis (53 studies) on the diagnostic accuracy of clinical signs.[29] Conversely, the lack of a paroxysmal cough or the presence of fever rules it out (sensitivity 82-93%, specificity 19-21%). In children, post-tussive vomiting was found to be less helpful in making a clinical diagnosis (sensitivity 60%, specificity 66%).

Box 1: Clinical criteria for diagnosing pertussis[24-26]

Cough lasting for at least two weeks with at least one of the following symptoms:

- Coughing paroxysms or fits
- Inspiratory whooping
- Post-tussive vomiting without other apparent cause
- Apnoea with or without cyanosis for infants <1 year old

What other diagnoses should I consider?

Consider other conditions causing acute cough (<3 weeks) and chronic cough (>8 weeks). Respiratory infections present acutely and are often associated with other symptoms such as purulent sputum production and fever. Asthma, cough-variant asthma, cystic fibrosis, and *Mycoplasma* or adenovirus infection may cause chronic cough.[30 31] Non-respiratory causes such as allergic rhinitis and gastro-oesophageal or laryngo-oesophageal reflux may also present with cough.[30 31]

What investigation to request?

Pertussis can be diagnosed clinically, and diagnostic testing should not delay treatment, especially in low resource settings.[32] Testing will allow confirmation of the diagnosis and is helpful for immunotyping and surveillance, especially during an outbreak. The infographic shows suggested investigations based on the duration of cough and patient's age.[33 34] Timing the tests in relation to the onset of symptoms is important as delay often decreases test accuracy, and a negative test result may be falsely reassuring (fig 2).

Culture

Nasopharyngeal bacterial culture obtained from a throat swab or aspirate is the best method for diagnosis of pertussis[35] (sensitivity 58%, specificity 100%).[33 36 37] The sensitivity is lower beyond two weeks of illness and in older people because of lower bacterial loads,[33 38] resulting in higher risk of a false negative result. Oral fluid samples are less reliable because of the risk of microbial contamination.[33] Rapid transport of the specimen for testing is essential as *B pertussis* survival declines during transport.[39] Culture generally takes 4-5 days[36] but may take up to 12 days,[33] making it the slowest diagnostic modality.

Polymerase chain reaction (PCR)

PCR testing of nasopharyngeal specimens provides a rapid diagnosis, usually within hours,[32] and has a high sensitivity (77-97%) and specificity (88-97%).[33 36 37 40] While nasopharyngeal swabs have the highest sensitivity, some laboratories also accept nasal or throat swabs. Testing is ideally done within the first four weeks of illness.[38] Modern techniques such as real-time PCR (RT-PCR) have higher sensitivity, but there have been concerns about cross reactivity with other *Bordetella* species, such as *B holmensii*, as well as inability to differentiate between live or dead bacteria, which may cause a false positive diagnosis.[33 39 41] Improved PCR techniques such as four-target RT-PCR are being developed to avoid cross reactivity.[42]

Serology

Testing for IgG to the pertussis toxin can be performed two weeks after the illness and up to the eighth week.[26 43] The results with testing blood (sensitivity 88-92%, specificity 98-99%)[44] or oral fluid or a throat swab (sensitivity 80%, specificity 97%)[45] are comparable. Oral fluid testing is easier to perform, especially in children,[46 47] but this medium is not often available in primary care and may instead be issued by public health agencies directly. Serology is not advised in infants and in patients vaccinated within the previous year, as the test cannot differentiate vaccine induced or maternal antibodies from infection induced antibodies.[33 48]

What are the risks?

Infants have a high risk of mortality due to pulmonary hypertension and resultant cardiac failure and shock.[1 8 49 50] Children are prone to dehydration and anorexia. Rarely, seizures and encephalopathy have been reported.[1 15 22 23] Acute cough-related complications include pneumothorax, aspiration, urinary incontinence, and increased risk of rib fractures, particularly in older adults.[23] Patients may develop sinusitis, secondary bacterial pneumonia, and otitis.

Parents may worry about the risk of asthma and other respiratory infections[51] in a child with a history of pertussis. Long term follow-up data do not suggest an increased asthma risk in adulthood.[52-54] Small studies have suggested possible intellectual impairment[55] and slight increased risk of developing epilepsy[56] after childhood pertussis, but these studies are underpowered and lack long term follow-up.

When to refer?

Urgently refer infants under the age of 6 months with suspected pertussis for hospitalisation because of a higher risk of complications and mortality. There is no guidance on referring older children and adults with suspected or confirmed pertussis. It is prudent to refer patients with signs of cardiorespiratory compromise, including apnoea and cyanosis; those with pre-existing respiratory conditions; and signs of complications such as dehydration, pneumonia, or encephalopathy.[9]

How is it managed?

No medications provide symptomatic relief from pertussis-associated cough. Antibiotics eliminate *B pertussis* from the nasopharynx and reduce the risk of transmission. They have not, however, been shown to reduce the duration or severity of cough. A Cochrane systematic review (12 randomised controlled trials, 578 adults and children) found no benefit of treatments such as oral diphenhydramine, intravenous pertussis immunoglobulin, or inhaled salbutamol on the frequency of coughing paroxysms compared with placebo.[60] There was no effect on frequency of vomiting, whoop, or cyanosis during coughing, or on serious complications such as seizures or mortality. Most trials were small. There were insufficient high

quality data to evaluate the efficacy of intramuscular or oral corticosteroids.

Preventing transmission

Explain the role of antibiotics and initiate treatment in patients with suspected or confirmed pertussis within 21 days of symptom onset. Beyond the first 21 days of illness, or two days of antibiotic treatment, patients are no longer infectious.[26 57 58] Azithromycin taken for 3-5 days, or clarithromycin or erythromycin taken for seven days are as effective as previously recommended longer regimen lasting 14 days, and have fewer side effects, suggests a Cochrane systematic review (11 randomised controlled trials).[59] Be aware of potential drug interactions of macrolides in patients taking medications such as theophylline or warfarin.[58] Co-trimoxazole is recommended for patients allergic to macrolides.

Advise patients who attend or work in nurseries, schools, and healthcare settings to refrain from attending for 48 hours after initiation of antibiotics, or for 21 days from onset of symptoms.[26] Exclusion may be difficult in social care settings such as care homes, and isolation may be more appropriate, with guidance from local public health agencies. Offer vaccination to unimmunised and partially immunised children under the age of 10 years after recovery.[26 43]

Report suspected cases to local public health agencies, even while diagnostic test confirmation is awaited, to facilitate tracing of contacts and timely chemoprophylaxis. Only 11% of pertussis cases (n=9163) in England between 2010 and 2015 were reported within 21 days of cough onset.[57]

Pregnant women

Avoid antibiotics in the first trimester of pregnancy. They may be advised later in the pregnancy if there is risk of transmission to vulnerable close contacts. They have limited benefit for the affected woman. If the woman is affected in the last month of pregnancy, erythromycin is recommended to prevent neonatal transmission.[26]

What measures are needed in close contacts of the patient?

Offer antibiotics to household contacts within 21 days of disease onset of the index case.[43] Chemoprophylaxis is also advised for other close contacts of the patient who work or live with them and are at high risk (people with pre-existing health conditions such as asthma or immunodeficiency, unimmunised or partially immunised infants, and pregnant women over 32 weeks' gestation).[26 43]

Encourage unimmunised or partially immunised contacts less than 10 years of age to complete the course of primary immunisation, and offer a booster dose to contacts above 10 years old who have not received a dose in the past five years.[26]

How can it be prevented?

Primary immunisation

Vaccination is estimated to have prevented 78% of disease-associated mortality and 1.3 million deaths worldwide, presumably by reducing incidence of pertussis.[61] Most countries complete three primary vaccinations in the first 6 months of life with boosters given thereafter.[5 7]

Several high income countries have switched from whole cell to acellular pertussis vaccines because of their decreased reactogenicity and better adverse effect profile. The evidence on relative effectiveness and duration of active immunity of the vaccines is inconsistent.[5 62] A recent meta-analysis found lower short term protective effect with acellular vaccines (vaccine efficacy 84% (95% confidence interval 81 to 87)) compared with whole cell vaccines (94% (88 to 97)) within three years of completion of primary immunisation.[63] The effectiveness of acellular pertussis vaccine decreases with time,[64] as reported in several case-control studies.[65-69] The short protection provided by vaccination suggests the possibility of repeated infections in both immunised and non-immunised individuals. The need for regular pertussis boosters throughout life must be explored.[70] A new genetically inactivated acellular vaccine is being studied in adolescents.[71]

The World Health Organization recommends that countries using whole cell pertussis vaccine should continue to do so and consider a switch to the acellular vaccine only if additional periodic booster or vaccination in pregnant women can be assured and sustained.[5]

Vaccination in pregnancy

Pertussis vaccination in pregnancy may provide passive immunity to the infant via transplacental transfer of IgG, before primary immunisation.[72 73] Assure women that the vaccine is safe in pregnancy. Safety studies covering over 150 000 women vaccinated in the second or third trimester show no increased risk of maternal adverse events and congenital anomalies in infants.[89] A slight increased risk of chorioamnionitis has been observed with acellular pertussis vaccine in large cohort studies in the United States,[90 91] but this was not associated with adverse neonatal outcomes. There is no evidence of increased risk of perinatal outcomes such as stillbirth or preterm birth in large cohort studies.[90-92]

Qualitative studies among pregnant women point to a need for healthcare professionals to discuss vaccination and offer it as part of routine antenatal care.[80-83]

The optimal timing of maternal pertussis immunisation is not established. Observational studies indicate that pertussis vaccination in the third trimester reduced infection, hospitalisation, and mortality in infants compared with no vaccination in pregnancy.[74-78] A large British retrospective cohort study using primary care data demonstrated that the benefit of passive maternal immunity did not persist beyond the third dose of primary immunisation in the infant.[79] Guidelines from Public Health England[26] and Centers for Disease Control and Prevention[84] recommend vaccination at 16-32 weeks and 27-36 weeks of gestation respectively. Immunisation in the second trimester may be preferred as it can protect preterm infants, allow more time for maternal antibody transfer, and can logistically be combined with a routine antenatal check.[85-87] Offer vaccination in every pregnancy as maternal antibody titres decrease rapidly after delivery.[88]

An alternative strategy, called "cocooning," is thought to prevent pertussis indirectly by vaccination of household adolescent and adult family members who may be a source of infection for infants.[84] The results have been mixed and do not support the universal implementation of cocooning.[93-96] A recent Australian trial (440 infants) found vaccination at birth to be safe and immunogenic.[97] Neonatal immunisation may offer an alternative to maternal vaccination to prevent pertussis in infants.

A parent's experience: a patient perspective

In mid-January 2017, our 4 year old daughter developed a mild cough. The previous week she had a mild temperature and a cold, and we thought little of it. After a week, her cough seemed to worsen, especially at night, waking her regularly and leaving her tired during the day. We became concerned her symptoms might relate to some early signs of asthma. A few days later, her cough became really violent, lasting 10-15 seconds and finishing with a vomit of large amounts of phlegm. Any running around seemed to bring on the coughing attacks.

On searching the internet, we realised that vomiting after coughing was often seen in whooping cough. We saw our GP, who took back-of-throat swabs from our daughter and prescribed us all prophylactic antibiotics. Our daughter had received all her infant vaccines and was due for her pre-school booster, so we thought getting whooping cough was unlikely. The following day we were contacted by Public Health England, who asked us details of our daughter's recent contacts, the name of her nursery, and provided some cautionary advice about future contacts until we had all completed a three day course of antibiotics. Parents were subsequently contacted via our nursery to be aware of whooping cough symptoms, and encouraged to organise a pre-school booster. A week or so later, our GP contacted us to say her whooping cough had been confirmed.

It is now May 2017, and our daughter still has a mild cough, which is set off by any exertion. She was back at nursery within two weeks from us first visiting the GP. Vomiting happens less, but whenever she gets a cold, the coughing-vomit cycle will pick up again. Otherwise she is fine, but after four months is still not completely clear of the symptoms. One of the interesting aspects for us is the reaction from other parents, and how it stirred up concerns regarding vaccination. We were surprised how many, in the face of explicit public health advice, still actively decided against pre-school booster vaccination.

As parents, it was good to know that our daughter's earlier vaccinations would have offered some protection from her developing more severe symptoms, although we do feel guilty that we hadn't organised her pre-school booster earlier. We are grateful for the reassurances from our GP that this episode will have no discernible impact on her risk of getting asthma or being vulnerable to future infections. We were a little surprised how few long-term outcomes studies were available to provide evidence to support this.

There may a greater need to refresh the memories of how big an effect even the more benign, vaccine-preventable diseases can have, and how little is known about their long term impact.

How patients were involved in the creation of this article

We consulted a parent whose child was affected by pertussis at the article planning and completion stage, who suggested that we discuss long term sequelae of pertussis. The parent of a child with pertussis contributed the patient perspective. One of the authors who was affected by pertussis suggested discussing treatment of pertussis-associated cough. We are grateful for the contribution of patients to the construction of the article and for providing a thought provoking perspective.

Additional resources for healthcare professionals

- Public Health England. Guidelines for the public health management of pertussis in England. 2018. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/762766/Guidelines_for_the_Public_Health_management_of_Pertussis_in_England.pdf.
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Education into practice

- How would you ask about cough in patients with symptoms for two weeks or more?
- Review your clinic or practice records for women booked for antenatal care to see if vaccination during pregnancy is consistently discussed or offered.
- Think about the last time you talked to a parent (on behalf of child) or patient about declining vaccination based on research on the Internet. How would you provide a balanced view of the benefits of pertussis vaccination? What resources could you use?

Contributors: All authors take full responsibility for the manuscript.

Competing interests: We have read and understood BMJ policy on declaration of interests and have no relevant interests to declare.

Funding: JB and DPG are supported by locally funded academic clinical fellowships.

Provenance and peer review: Commissioned; externally peer reviewed.

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Figures

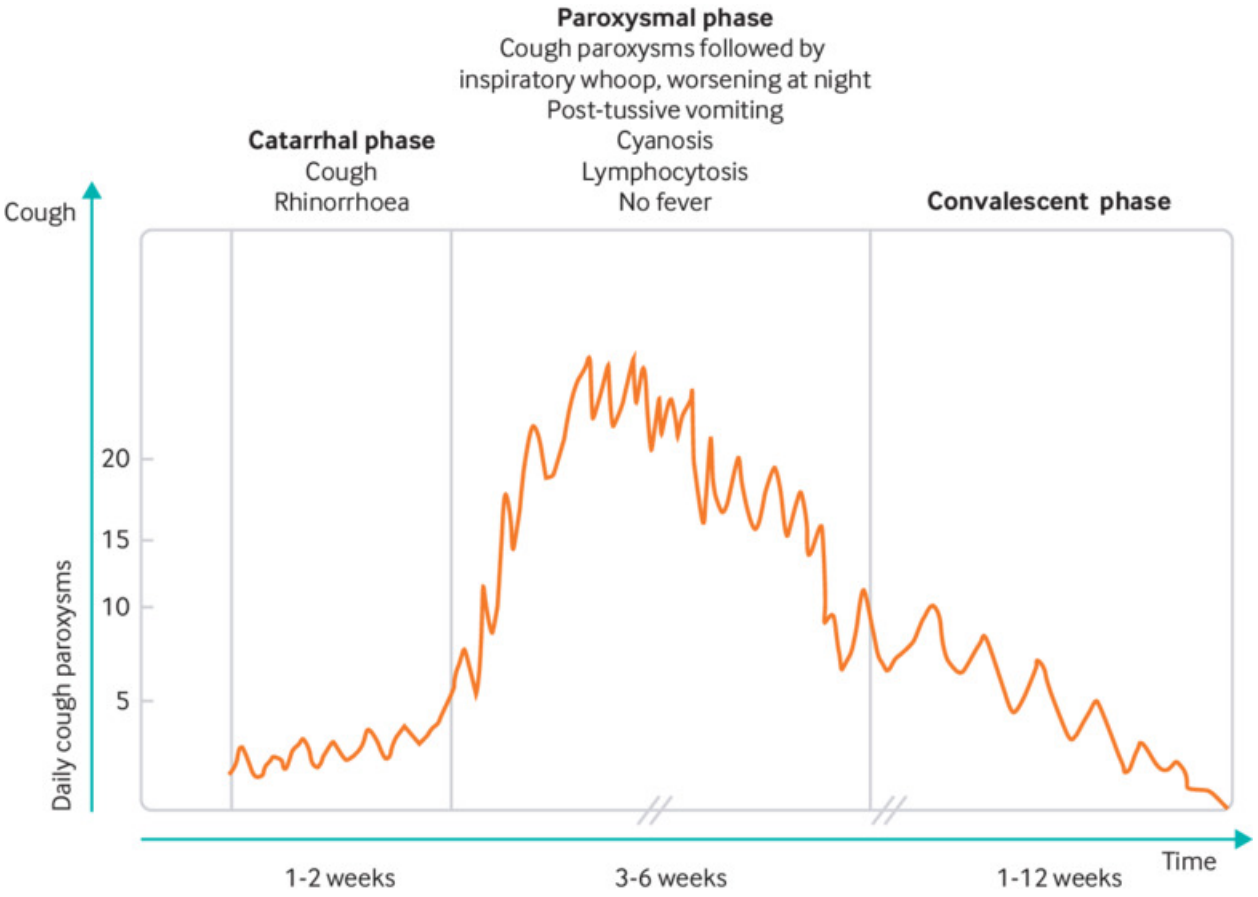

Fig 1 Diagrammatic representation of the frequency of daily cough paroxysms against clinical course of pertussis.[17] Reproduced with permission from the World Health Organization

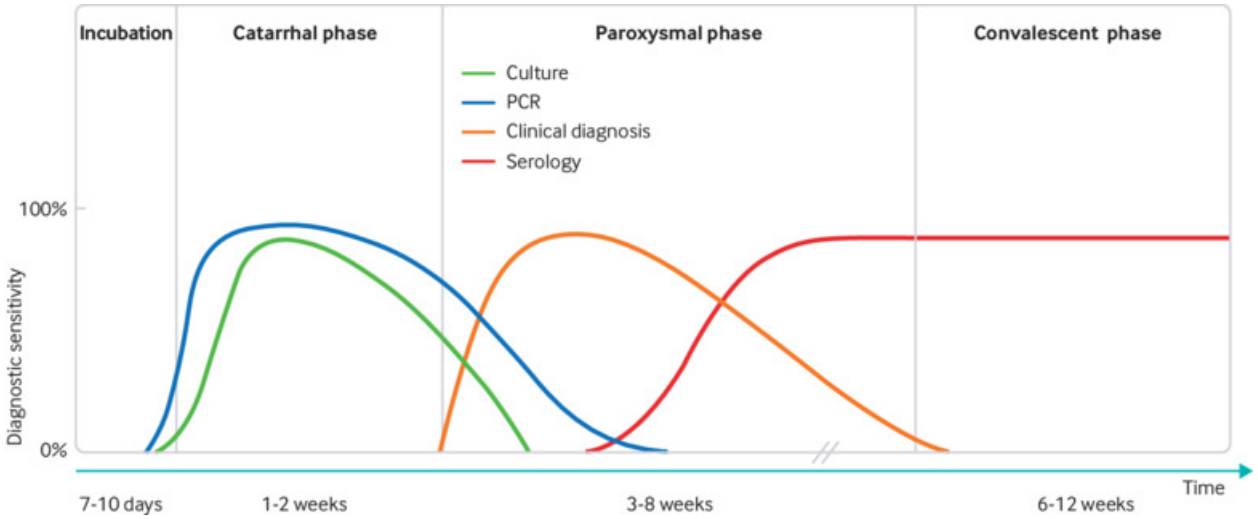

Fig 2 Relative diagnostic sensitivities of culture (green), polymerase chain reaction (PCR) (blue), clinical diagnosis (orange), and serology (red) and during different stages of *B pertussis* infection. The represented sensitivities were idealised for clarity.[33] Reproduced with permission from the American Society of Microbiology