



The Re-emergence of Pertussis: Diagnostic and Public Health Perspectives



Further information:

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Increasing awareness of atypical pertussis

Pertussis, or whooping cough, is a highly contagious respiratory tract infection caused by the bacterium *Bordetella pertussis* and sometimes referred to as the “100-day cough”. The virulence factors of *Bordetella* species are presented in Table 1. The reproductive rate (the average number of secondary infections directly resulting from one infection in a completely susceptible population) of whooping cough is ~15, making it one of the most contagious directly transmitted human pathogens. Like many serious diseases, pertussis is preventable through routine childhood vaccination. However, despite more than half a century of vaccination, it remains endemic in Australia, causing epidemic outbreaks every 3 to 5 years.

Virulence factors	<i>B.pertussis</i>	<i>B.para-pertussis</i>	Composition of pertussis vaccines licensed in Australia (µg/dose)	
			Infantri x	Tripacel
Pertussis toxin	+	-	25	10
Pertactin	+	+	8	3
Filamentous agglutinin	+	-	25	5
Fimbrial adhesin	+	+	-	2
Adenylate cyclase	+	+	-	-
Dermatonecrotic factor	+	+	-	-
Tracheal cytotoxin	+	+	-	-
Tracheal colonisation factor	+	-	-	-

Table 1. Virulence determinants of *Bordetella pertussis*

Pertussis infections have a wide spectrum of clinical expression and are affected by patient age, previous exposure to the microorganism, antimicrobial treatment and the presence of cross-reacting antibodies. Pertussis can range from an asymptomatic infection in children and adults with strong residual immunity to a more severe and life-threatening disease in unprotected newborns and young infants. Although children continue to experience the worst morbidity from recognised primary *B.pertussis* infection, reported rates of infection have increased most noticeably in previously vaccinated adolescents and young adults. Vaccine changes, shifts of pertussis serotype, and waning vaccine-induced immunity have contributed to the shift in the age distribution of cases. International studies indicate that 12-32% of adolescents with a coughing illness lasting at least 1-2 weeks are infected with *B.pertussis*.

Another potential confounding issue regarding the increasing incidence of pertussis is that of infection by *B.parapertussis*. This microorganism is equipped with similar virulence factors, and may cause disease similar to mild pertussis. It appears that pertussis vaccines offer little protection against *B.parapertussis* because of slight differences in the molecules of pertactin, filamentous agglutinin and fimbriae expressed by *B.pertussis* and *B.parapertussis*. Unless specific PCR is used, it may be difficult for diagnostic laboratories to distinguish between infections caused by these two *Bordetella* species.

Laboratory confirmation of a clinical diagnosis

Laboratory confirmation of diagnosis by polymerase chain reaction (PCR) or serology should be attempted, especially when atypical pertussis is clinically suspected. The use of PCR has made the rapid diagnosis of pertussis possible and offers a higher sensitivity compared with conventional culture. However, the sensitivity of PCR decreases with the duration of symptoms and it can be associated with occasional false positive results caused by contamination at various stages (from sample collection to the laboratory).

Natural infection with *B.pertussis* is followed by an increase in serum concentration of IgA, IgG and IgM antibodies to specific antigens as well as to preparations of the sonicated whole organism usually used in commercial diagnostic assays. In contrast with natural infection, primary immunisation induces mainly IgG and IgM antibodies. The greatest specificity for the serological diagnosis of *B.pertussis* infection is achieved by measurement of IgG and IgA antibodies to pertussis toxin. The demonstration of IgA and IgG to pertussis toxin, pertactin or whole cell antigen suggests recent infection with *B.pertussis*. Serology is more useful for diagnosis in adolescents and adults as some culture-positive children, particularly infants, fail to develop measurable antibodies. The younger the child, the less consistent is the IgA antibody response.

Methods of detecting pertussis still need improvement and significant underreporting of pertussis exists among adolescents and adults. The use of PCR in combination with serology is recommended as follows;

Duration of cough		
<2 weeks	2-4 weeks	> 4 weeks
PCR	PCR + Serology	Serology

Prevention of outbreaks

The pool of frequently undiagnosed pertussis cases in adolescents and adults provides a reservoir for potentially serious infections in infants who are either unvaccinated or whose vaccinations are not yet fully protective. The relative role of adolescents and adults in transmitting *B.pertussis* infection to infants appears to increase with increasing vaccination coverage and with the duration of the vaccination program and reaches levels of >50% of all transmission sources. Recently vaccinated children may still get pertussis infection and may then serve as reservoirs and potential transmitters. Breakthrough cases appear to be less infectious than cases in unvaccinated children and asymptomatic infection with *B.pertussis* is thought to contribute little, if anything, to pertussis transmission and community outbreaks.

Efforts to achieve control of outbreaks of pertussis in a community are costly and require intensive surveillance, detailed alerts to health care professionals, enhanced communication and public education, and aggressive measures involving treatment, prophylaxis and the isolation of suspected cases.

New pertussis variants and epidemiological typing

A systematic review of the effects of pertussis vaccines on children conservatively estimated absolute efficacy of three or more component acellular vaccines as 80-84%. It has also been suggested by several groups of researchers that isolates circulating in a community may be antigenically distinct from

vaccine strains and from those circulating before the introduction of the pertussis vaccination. Recent evidence from Europe and Australia suggests that we do face the emergence of successful clones of *Bordetella* harbouring new variants of pertussis toxin.

During the past decade, the demonstration of polymorphism in *B.pertussis* genes encoding the expression of pertactin and pertussis has led to the suggestion that vaccine-driven evolution has resulted in decreased vaccine efficacy. It is of concern that strains of *B.pertussis* currently circulating in the population may have diversified from the very limited number of strains used in vaccines, so that vaccine-induced immunity does not fully protect against current disease-causing strains. Yet other factors, such as greater awareness, better diagnostics and the suboptimal efficacy of vaccination schedules are also likely to contribute to the increased reporting of pertussis.

To control pertussis, the variation of virulence factors of strains circulating in the population has to be monitored. However, determination of these variants is currently performed using time-consuming and expensive sequence analysis. There is a need for new approaches to direct detection and characterization of microorganisms with epidemic potential. Realising this problem, the Centre for Infectious Diseases and Microbiology – Public Health has been developing methods for the molecular subtyping of *B. pertussis*.

References are available on request from the author.

Grant Successes

Richard Russell is a Collaborating Investigator on a project recently awarded AUD\$10,000,000 over 5 years from the 'Grand Challenges in Global Health Initiative' funded by the Foundation NIH / Gates Foundation / Wellcome Trust, and the University of Queensland. The multinational team, with scientists from Australia, USA, Japan, Thailand and Vietnam, is led by Prof Scott O'Neill from the University of Queensland, and has the objective of 'Modifying Mosquito Population Age Structure to Eliminate Dengue Transmission'. The project will introduce a bacterial parasite (a *Wolbachia* endosymbiont) that occurs naturally in other insects into mosquitoes so that it causes them to die before they are old enough to transmit the virus, with the mosquitoes inheriting the parasite and passing it from generation to generation.

Australian Research Council Linkage Grant: "Informatics approaches to improving risk assessment and response to outbreaks of communicable diseases". Investigators on the project are: Dr Vitali Sintchenko, Professor Enrico Coiera, Professor Lyn Gilbert, Mr David Moscatello, Ms Heather Gidding, Dr Dominic Dwyer and Mr Mark Bartlett. A partnership between CIDM-PH, the Centre for Health Informatics, University of NSW, NSW Department of Health and the Commonwealth Department of Health and Ageing - this project will develop and test a new model of outbreak detection and risk assessment. The model addresses the need for improvement in the timeliness and specificity of early detection and control of biothreats; in particular the detection of infections caused by category A biological agents which pose a risk to national security. The project will contribute to research priority 4 "Safeguarding Australia from invasive diseases and securing our critical infrastructure".

STAFF PROFILE BELINDA HERRING



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Belinda completed her PhD at the University of Sydney/WMMI in 2001 working on molecular epidemiology and genetic diversity and evolution of HIV-1 genes. She then took up a postdoctoral position at the University of Washington and then UCSF - San Francisco where her research focus broadened to include other RNA viruses such as Hepatitis C and West Nile Virus. Belinda commenced at CIDM-Public Health as a research virologist in 2004 and has initiated a research program looking at molecular epidemiology and genetic variation of Ross River virus (see below) which is gradually expanding to include other arboviruses relevant to human health. Belinda also has an interest in norovirus and is examining the molecular characteristics of the recent (2004) gastroenteritis outbreak in NSW.

Ross River virus (RRV) is an important human pathogen that is found exclusively in Australia, Papua New Guinea and the South Pacific; including the Solomon Islands and Fiji. RRV is transmitted from vertebrate hosts to humans via mosquitoes and causes a systemic febrile illness in humans. Whilst not fatal, the disease causes significant economic losses due to the inability of infected individuals to work and symptoms may persist for many months.

The most important mosquito vectors of RRV in Australia are *Aedes sp.* in coastal areas and *Culex sp.* and *Coquillettidia sp.* in inland areas. Slight changes in the envelope gene may allow the virus to evade or escape the immune response. Changes in the envelope genes and other genes are useful as epidemiological tools as viral variants separate when subjected to phylogenetic analysis according to these mutations. Previous studies of the phylogenetic relationships of RRV in different geographic locations in Australia and the South Pacific identified a number of genetic groups however a contemporary analysis of genetic variation of RRV is lacking. The aim of this research work is to examine genetic variation of RRV in NSW. The clinical importance genetic variation is not known, however identification and genetic analysis of these variants, in conjunction with clinical data, will shed more light on the story of RRV infection.

CIDM PUBLIC HEALTH EDUCATION PROGRAM

The CIDM Public Health Education Program for 2006 is being finalised (months are provisional at this stage).

- Sexually Transmissible Infections (March)
- Influenza Workshop (May)
- Vaccine Preventable Diseases (August)
- Antibiotic Resistance (November)

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