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Review

Bordetella pertussis epidemiology and evolution in the light of pertussis resurgence

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ABSTRACT

Whooping cough, or pertussis, is resurgent in many countries world-wide. This is linked to switching from the use of whole cell vaccines to acellular vaccines in developed countries. Current evidence suggests that this has resulted in the earlier waning of vaccine-induced immunity, an increase in asymptomatic infection with concomitant increases in transmission and increased selection pressure for *Bordetella pertussis* variants that are better able to evade vaccine-mediated immunity than older isolates. This review discusses recent findings in *B. pertussis* epidemiology and evolution in the light of pertussis resurgence, and highlights the important role for genomics-based studies in monitoring *B. pertussis* adaptation.

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1. Pertussis

Bordetella pertussis is a gram-negative bacterium that causes the serious respiratory disease whooping cough, or pertussis. Often considered a disease affecting only children, it is now clear that all ages are affected but young infants are at greatest risk of severe pertussis as a result of their immature respiratory systems and being too young to have received the full course of vaccination. Infection begins with acquisition of *B. pertussis* by the inhalation of contaminated aerosol droplets (Mattoo and Cherry, 2005). Pertussis is commonly described as progressing through three stages. Initially symptoms are non-specific, such as rhinitis and cough. The frequency and severity of cough builds

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into the paroxysmal phase. These characteristic paroxysmal coughs that are the hallmark of classic pertussis occur multiple times every hour and continue for a number of weeks. They leave the host exhausted and gasping for air, producing a "whoop" like sound when they try to inhale after a coughing fit. Frequently vomiting follows paroxysms. Complications associated with pertussis include seizures and encephalopathy. In the most severe cases, pulmonary hypertension can result in cardiac failure and death (Paddock et al., 2008). A convalescent phase is associated with the lessening of cough symptoms.

2. Vaccination

In the first half of the 20th century, pertussis was an endemic childhood disease worldwide. For example, in the UK there were many tens of thousands of cases each year, with peaks every 3–4 years, Fig. 1. The first pertussis vaccines were developed during the 1930s and implemented in most developed countries during the 1940s and 50s (Cherry, 1996). These were whole cell vaccines (WCVs) comprised of chemically killed bacteria. They were administered in combination with diphtheria and tetanus toxoids, with a full course of vaccination comprising three injections during the first six months of life. Following the introduction of vaccination there was a very large reduction in the incidence of disease, demonstrating that WCVs were extremely effective at preventing classic pertussis, i.e. whooping cough in infants and children, which was certainly the main recognised form of *B. pertussis* infection at that time. The introduction of vaccination globally has been a major success. Monitoring by WHO recorded around 140,000 cases of pertussis globally in 2014, resulting in 89,000 deaths (WHO, 2014). Although this probably represents under-reporting it nevertheless signifies a tremendous reduction in disease burden compared to the pre-vaccination era. However, WCVs were considered 'reactogenic', causing side effects including fretfulness and injection site soreness and swelling. In particular more serious complications began to be associated with pertussis vaccination including seizures, other neurological sequelae and even sudden infant death (Cherry, 1992). The evidence for and against 'pertussis vaccine encephalopathy' has been reviewed extensively (for example Mattoo and Cherry (2005)). The data probably describes a situation in which infantile epilepsy begins to manifest and peak sudden infant death syndrome incidence occurs when they will be temporally associated with pertussis vaccination, but in which there is no cause and effect relationship. Unfortunately a growing public distrust of the vaccines led to dramatic decreases in vaccination coverage. For example, in the UK coverage was as low as 31% during the period 1975–8. This was followed quickly by significant pertussis epidemics. Combined, these scenarios spurred the development of a second generation of pertussis vaccines, the acellular vaccines (ACV). These comprise a number of highly purified *B. pertussis* proteins: pertussis toxin (PT), filamentous haemagglutinin (FHA), pertactin (Prn), and fimbrial proteins 2 and 3 (Fim2 and 3). A number of mono-, bi- and multi-antigen ACVs have been developed but the most commonly used contain either PT, FHA and Prn, or all five antigens. Detailed reviews of these vaccines are available elsewhere (for example see (Decker and Edwards, 2000) but briefly their efficacy to prevent pertussis appears to be slightly lower than that of WCVs but they have better safety profiles than WCVs in terms of causing reactions. Importantly, the immune responses stimulated by WCV and ACV differ, being Th1/Th17 biased vs Th2/Th17 biased respectively (Ross et al., 2013). The consequences of this for host immunity–pathogen interactions are unknown, but seemingly they are contributing to the resurgence of pertussis (see below). Initially introduced as booster vaccinations following primary inoculation with WCV, many developed countries switched to the use of ACVs for the entire vaccination course at the end of the 1990s and the early 2000s. Much of the developing world continues to use the cheaper WCVs.

3. Pertussis resurgence

During recent years a number of countries, including the U.S., U.K., Australia and the Netherlands, have experienced an increase in the incidence of pertussis, including a number of significant outbreaks (Burns et al., 2014). For example, the UK suffered an outbreak in 2012, in which 9711 laboratory-confirmed cases were recorded in England and Wales (Fig. 2), leading to fourteen deaths in infants less than 3 months

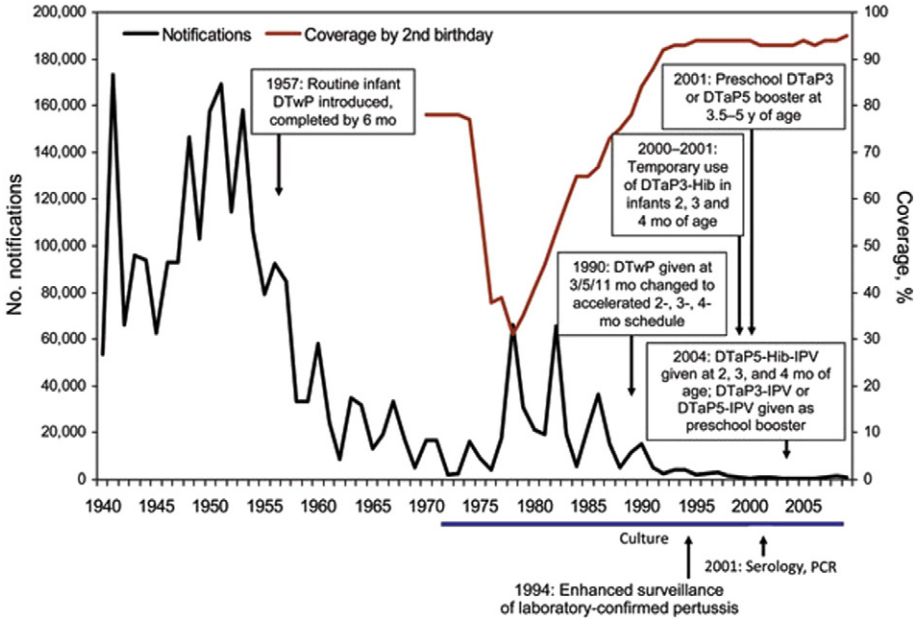

Fig. 1. The number of notifications of pertussis and vaccine coverage (% of children <2 years vaccinated) from 1940–2009 in England and Wales. The major changes in vaccines and schedules for pertussis vaccination are indicated as are the use of culture, serology and PCR for diagnoses. DTwP: diphtheria/tetanus/pertussis (WCV) vaccine; DTaP3: diphtheria/tetanus/pertussis (3 component ACV) vaccine; DTaP5: diphtheria/tetanus/pertussis (5 component ACV) vaccine; DTaP3: diphtheria/tetanus/pertussis (3 component ACV) vaccine; DTaP3-Hib: diphtheria/tetanus/pertussis (3 component ACV)/*Haemophilus influenzae* type b vaccine; DTaP3-Hib-IPV: diphtheria/tetanus/pertussis (3 component ACV)/*Haemophilus influenzae* type b/inactivated polio vaccine; DTaP3-IPV: diphtheria/tetanus/pertussis (3 component ACV)/inactivated polio vaccine; DTaP5-IPV: diphtheria/tetanus/pertussis (5 component ACV)/inactivated polio vaccine; DTaP5-Hib-IPV: diphtheria/tetanus/pertussis (5 component ACV)/*Haemophilus influenzae* type b/inactivated polio vaccine.
Reproduced from Campbell et al. (2012)).