MINIREVIEW

What to do about pertussis vaccines? Linking what we know about pertussis vaccine effectiveness, immunology and disease transmission to create a better vaccine

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One sentence summary: This review discusses various limitations of the current approaches to protection from pertussis.

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ABSTRACT

Pertussis (whooping cough) is a respiratory disease caused by the bacterium *Bordetella pertussis*. Despite the implementation of immunization programs and high vaccine coverage in most jurisdictions, pertussis is still one of the most common vaccine-preventable diseases, suggesting that the current vaccines and immunization schedules have not been sufficiently effective. Several factors are thought to contribute to this. The acellular pertussis vaccine that has been used in many jurisdictions since the 1990s is less effective than the previously used whole-cell vaccine, with immunity waning over time. Both whole-cell and acellular pertussis vaccines are effective at reducing disease severity but not transmission, resulting in outbreaks in vaccinated cohorts. In this review, we discuss various limitations of the current approaches to protection from pertussis and outline various options for reducing the burden of pertussis on a population level.

Keywords: Pertussis; whooping cough; vaccine; vaccine effectiveness; transmission; immunity

INTRODUCTION

Recurrent pertussis outbreaks in the USA, France, UK and the Netherlands (Mooi *et al.* 2009; Billingsley 2012; Centres for Disease Control and Prevention 2012, 2013a; Cherry 2012a; Winter *et al.* 2012; Guiso 2014; Health Protection Agency 2013) as well as a persistent upward incidence trend in several jurisdictions (Guris *et al.* 1999; Tanaka *et al.* 2003) provide accumulating evidence that immunization programs using acellular pertussis (aP) vaccines have not been the success they were hoped to be. Several hypotheses have been presented to explain the resurgence of pertussis cases, including reduced vaccine effectiveness, a waning immune response that is mismatched to the pathogen, suboptimal vaccine coverage and ongoing transmission in

vaccinated individuals (Burns, Meade and Messionnier 2014). It is likely that, rather than one of these being the reason for the shortcomings of the aP vaccine, several factors are responsible (Burns, Meade and Messionnier 2014). It is time to go back to basics in order to move forward in achieving the primary aim of pertussis immunization programs—to protect infants who have not completed their primary immunization series from severe disease (World Health Organization 2010). In achieving this, we may also succeed at secondary aims, like reducing morbidity and transmission in older age groups. New thinking and a new strategy is needed that is informed by a multidisciplinary approach to the challenges presented by this fascinating organism.

REDUCED EFFECTIVENESS OF THE aP VACCINE

Compared with the best whole-cell pertussis (wP) vaccines, aP vaccines are not as effective in mass immunization programs (Vickers *et al.* 2006; Cherry 2012b), although their success in having far fewer reactions than were associated with wP vaccines (Zhang *et al.* 2014) should not be discounted. Recent studies of outbreaks in highly immunized populations have shown that the duration of protection of aP vaccines is too short (Klein *et al.* 2012; Misegades *et al.* 2012), resulting in a decrease in immunity in older children and adolescents, and a corresponding increase in cases in this age group (Skowronski *et al.* 2002; Klein *et al.* 2012). This is in contrast to wP vaccines, which provide protection well into the teenaged years (Klein *et al.* 2012). As a result of these shortcomings, in countries that switched to the aP vaccine in the 1990s we now have a generation of children not only less well-protected against pertussis but who may also be less responsive to boosters, since the vaccine with which a child is primed may determine their immune response to later booster vaccination (Podda *et al.* 1995; Mascart *et al.* 2007; Sheridan *et al.* 2012; Liko, Robison and Cieslak 2013; Smits *et al.* 2013).

WANING IMMUNITY TO PERTUSSIS OVER TIME

Progress in understanding the immunology of pertussis vaccines has been hampered by the lack of a simple humoral correlate of protection (Plotkin 2014); a standard used by industry and regulators for assessing vaccine efficacy (Olin *et al.* 2001). That aP vaccines are less successful in eliminating pertussis than wP vaccines illustrates the limitations arising from the lack of a relevant correlate of protection (humoral or cell mediated), or method of assessment that could be standardized. It is known that, unlike natural infection and wP vaccination, aP vaccines do little to engage cellular immunity and Th1 responses, which, in addition to Th17 responses, have been shown to be essential for clearance of *Bordetella pertussis* and may be the key to sustained protection (Ryan *et al.* 1998; Higgs *et al.* 2012; Ross *et al.* 2013). At the same time, the aP vaccine stimulates a robust Th2 response, perhaps partially due to the fact that aP vaccines are adjuvanted by alum, a Th2 stimulator (Ross *et al.* 2013). This is in contrast to wP vaccines, which include the Th1 inducer lipopolysaccharide (Barton and Medzhitov 2002). The Th2 response elicited by aP vaccine results in high antibody levels, which do not necessarily correlate well with immunity (Olin *et al.* 2001). For example, although pertussis toxin (PT) antibodies are thought to be associated with protection (Cherry *et al.* 1998), PT antibody levels induced by aP are much higher than those induced by wP, even though protection is lower (Miller *et al.* 1991; Olin *et al.* 2001). Compounding the issue of a skewed Th2 immune response is waning immunity following aP vaccination.

Despite an initially strong response, antibody levels fall several fold between aP doses (Guerra *et al.* 2009). Cell-mediated immunity, including memory T cells, persists in aP recipients, but more robust lymphocyte proliferation and cytokine responses are observed in those primed with wP compared to aP (Smits *et al.* 2013). The emerging story appears to be that antibodies have an important role in controlling infection and disease, but they may not be sufficient, requiring other immune functions for durable protection. This could explain the year-on-year decrease in aP vaccine effectiveness that has been shown in older children and teens (Cherry 2012b; Klein *et al.* 2012; Witt, Katz and Witt 2012; Koepke *et al.* 2014; McGirr and Fisman 2015). However, without clear humoral and cellular correlates of protection, the significance of antibody decay and cell-mediated immunity in contributing to reduced effectiveness of the aP vaccine is not clear.

TRANSMISSION IN aP VACCINATED INDIVIDUALS

Pertussis outbreaks are cyclical, mediated by the balance between susceptible and immune individuals. When there are ample immune individuals (through vaccination or natural infection) in the population, there is little pertussis activity. When a susceptible cohort accumulates in the population (for example by birth or waning immunity), an epidemic threshold is reached and an outbreak occurs (Fine and Clarkson 1987). Theoretically, the introduction of vaccination should lengthen the interval between epidemics, since vaccination should keep a critical mass of immune individuals in the population. However, this has not been universally observed for pertussis. Many years ago, Paul Fine asked why the interepidemic period for pertussis in England did not seem to be changed by vaccination programs, with outbreaks occurring every three to four years both before and after vaccination was introduced (Fine and Clarkson 1982). Close examination of outbreak patterns revealed that, although the interepidemic period remained the same, the amplitude of disease cycles increased following periods of low vaccine uptake (Fine and Clarkson 1982, 1987), an epidemiological signal that the vaccine may not be controlling infection and disease transmission, but rather clinical disease severity. Conversely, following years of high vaccine uptake, cycles still followed the same pattern but morbidity was reduced.

Capturing the precise epidemiology of pertussis is challenging, because case reporting and the resulting estimation of morbidity in the population is not always accurate, and varies depending on several factors. For example, case reporting varies by age group, with underreporting being common in older children and adults (McGirr, Tuite and Fisman 2013), as well as by severity, with milder cases less likely to be reported. In addition, underreporting is more likely to occur during interepidemic periods, while more comprehensive case reporting usually occurs during outbreaks.

A recent, more nuanced, perspective has considered whether the vaccine affects transmission and to what extent (Gay and Miller 2000; Domenech de Celles *et al.* 2014). Although transmission is often the focus for epidemiologists, experiments by microbiologists and immunologists typically address disease. Vaccine design requires attention on both fronts, and pertussis vaccine studies in the laboratory must take this into account. A program that focuses on individual-level protection is unlikely to ever have the success of one that works through a combined individual and herd approach that targets both protection from

disease as well as transmission, such as that achieved for smallpox, polio, measles and rubella.

This perspective on the effect of immunization programs relates to the population biology of pathogens as well as host and to the centrality of herd immunity in explaining the success of immunization. It reveals a limitation of vaccine studies that are designed to test the protection conferred on the vaccinated individual but do not measure subclinical infections that can contribute to ongoing circulation. The positive examples of smallpox, polio, measles and rubella led to the logical conclusion that protecting an individual from disease necessarily resulted in an end to the chain of transmission. Pertussis demonstrates that this may not necessarily be true. Interrupting pathogen transmission is at the heart of herd immunity, since organisms only continue to survive if they continue to spread. Preventing onwards transmission may be achieved by vaccines that prevent or reduce disease symptoms (such as cough) that serve to transmit the pathogen. In the case of aP vaccines, the reduction of transmission in individuals recently vaccinated might be offset by the increased transmission that occurs because immunity wanes faster than immunity acquired through natural infection or wP vaccines. In order to conceptualize how we can intervene to prevent transmission, it is helpful to consider the series of challenges that organisms have had to overcome to avoid extinction in populations. Organisms seeking to survive must first develop mechanisms to infect their host, compete with resident bacterial flora and evade innate immunity to colonize and replicate using pathogen-specific virulence factors. To spread, organisms then induce symptoms that contribute to transmission (such as cough) to another susceptible person before the host's adaptive immunity catches up with them and without killing so many hosts that the host population (the pathogen's ecological niche) is disrupted. Pertussis remains remarkably successful despite extensive control efforts, underscoring the significance of understanding the mechanisms involved in its ability to both infect and transmit efficiently.

Prospects to elucidate the determinants of disease transmission have been improved by new animal models, which provide an experimental system in which the transmission process can be examined via a reductionist approach that can reveal the bacterial genes and host immune functions involved. Pertussis animal models have demonstrated that, although it is fairly effective at controlling disease, the aP vaccine is poor at controlling colonization, shedding and transmission. For example, the baboon model has recently been shown to mimic important aspects of symptoms and immune response to infection and, most excitingly, to demonstrate efficient transmission between animals over distance, presumably via aerosolized droplets believed to transmit *B. pertussis* between humans (Warfel, Zimmerman and Merkel 2014). The baboon model demonstrated that wP-vaccinated baboons rapidly cleared infection. Baboons vaccinated with aP vaccine were protected from severe diseases, but still colonized *B. pertussis* and transmitted it to other naïve baboons (Warfel, Zimmerman and Merkel 2014).

Unfortunately, various difficulties of baboon studies limit the number of experiments that can be performed. An experimental murine model has been developed using *B. bronchiseptica,* a closely related species to *B. pertussis* (Mattoo and Cherry 2005). These two bacteria share the ability to transmit between hosts via respiratory droplets, so the mechanisms involved are likely to be similar. In addition, since *B. bronchiseptica* shares four of the five antigens used in most aP vaccines (Pertacin, Fim 2 and 3, and filamentous hemagglutinin) (Smallridge *et al.* 2014), it is a suitable model in which to study pathogen–host interactions

and vaccine effects (Goebel, Zhang and Harvill 2009). This model mimics important aspects of bacteria–immune interactions that affect transmission amongst baboons and humans. For example, when mice were vaccinated with wP vaccine, both shedding and transmission were inhibited, but the aP vaccine was unable to inhibit either shedding or transmission. These observations from biology align very well with what we observe epidemiologically (Nicholson *et al.* 2012). The efficiency of the murine model will allow for the analysis of many candidate bacterial genes that might be involved in the transmission process. Many tools of mouse molecular immunology will also allow aspects of the host immune response that might inhibit, or contribute to, transmission to be identified. Most exciting is the prospect for using the combination of these systems to efficiently identify bacterial and host factors in mice, confirm their roles in a recently developed aerosol transmission experimental system in pigs (Nicholson *et al.* 2012) and verify their relevance to *B. pertussis* transmission in baboons.

THE ROAD FORWARD

Until better understanding provides a pathway to improved vaccines, it would be healthy to debate whether the minority of the world that has experimented with aP vaccines should seriously be considering a return to wP, or the introduction of a mixed wP/aP vaccine schedule, since this may be the fastest avenue to better control of pertussis. From an ethics perspective, there is a question whether we are in a state of clinical equipoise, whether as a clinician counselling individual patients or parents or at a program level and if we know that wP vaccines are more effective. But this is a hard topic to debate. How would we balance the risk of local reactions against the risk of vaccine failure? If we pushed to use a more effective vaccine with a worse safety profile, what would be the implications for public confidence?

In response to the evident limitations of the aP vaccine, encouraging progress is being made with evaluating alternative aP pertussis vaccination schedules. A cocooning strategy—vaccination of post-partum women and other household members of infants—was previously recommended in some jurisdictions (Kretsinger *et al.* 2006; McIntyre and Wood 2009), since studies suggest that household members and particularly parents were the most common source of pertussis transmission to infants (Wendelboe *et al.* 2007). However, due to logistical hurdles and questions about cost and effectiveness, cocooning has not been widely implemented (Terranella *et al.* 2013; Lim, Deeks and Crowcroft 2014; Fernandez-Cano, Armadans Gil and Campins Marti 2015).

Neonatal immunization has also been explored, and although it resulted in adequate antibody titres, there was evidence of reduced titres for several pertussis antigens by the end of the primary vaccination series (Halasa *et al.* 2008). Additionally, there was some concern about interference with immune responses to other antigens/vaccines (Knuf *et al.* 2010; Wood *et al.* 2010; Amirthalingam *et al.* 2014), suggesting that, should this intervention be applied, a single antigen pertussis vaccine would need to be developed (Burns, Meade and Messionnier 2014). A new consideration in pertussis immunology is the growing evidence that antenatal immunization protects infants, whether through indirect protection because mothers do not develop pertussis, or through direct protection of infants via antibodies in cord blood (Amirthalingam *et al.* 2014). Immunization in pregnant women is currently recommended in several countries (Centers for Disease Control and

Prevention 2013b; Olley 2014) due to transplacentral antibody transfer in utero (Gall, Myers and Pichichero 2011) and increased IgA in breastmilk (Halperin *et al*. 2011). This approach was shown to be highly effective when high coverage was achieved during a national outbreak in the UK (Amirthalingam *et al*. 2014). However, some concern remains about maternal antibodies potentially inhibiting pertussis antibody production in infants following vaccination (Amirthalingam 2013). In addition, in some jurisdictions maternal reimmunisation has been suggested at every pregnancy due to waning immunity, regardless of the interval between pregnancies or the last adult booster (Healy, Rench and Baker 2013; Abu Raya *et al*. 2015; McGirr and Fisman 2015). Finally, many countries offer a single adult pertussis-containing booster vaccine, which could be extended to regular boosters throughout adult life, anchored to our need for regular tetanus immunisation. It has been suggested that a decennial adult booster may be required to significantly reduce the burden of pertussis (Cherry 2010; McGirr and Fisman 2015), although some are skeptical (Fine 1997), studies have demonstrated that waning immunity results in reduced protection well before the 10-year mark (Healy, Rench and Baker 2013; Abu Raya *et al*. 2015). This approach would be potentially cost-effective (Lee, Riffelmann and Wirsing von Konig 2008), but may not be practicable. In the context of already suboptimal vaccination rates in many jurisdictions or in periods of low pertussis activity, the feasibility and acceptability of adult boosters and reimmunisation in every pregnancy is unclear (Cherry 2010).

It should be recognized that, without clear correlates of protection, the long-term effectiveness of each of the above interventions is uncertain. Furthermore, each of the approaches outlined above can be conceptualized as either targeting high risk (neonates) or low coverage (adults) groups and therefore unlikely to have the impact on the population biology of pertussis that could maximize benefits to health. They are not ideal approaches. We also need a long-term perspective on what will happen when the generation of aP primed individuals become parents. How will this affect this cohort's future experience of pertussis as adults, and what are the implications of this for their own children?

CONCLUSIONS

Research directed at developing effective vaccines that uncovers the mechanisms whereby natural infection and wP vaccine may yield better duration of immunity and prevent transmission should be an immediate priority. Essential to this is the determination of correlates of protection for pertussis, including both humoral and cellular correlates. A simple model of disease that works so well for other toxin-mediated diseases such as tetanus and diphtheria is too simple for pertussis. But a complex model may still be amenable to control by a simple and effective intervention that might emerge from a better understanding of the biology at individual and population levels. The results of this work would help elucidate the way forward.

Options under discussion include altering the current aP vaccination schedule, using a live-attenuated vaccine (Fedele *et al*. 2011), modifying the aP vaccine with new antigens and/or adjuvants, developing a completely new vaccine or returning to the wP vaccine. In considering these strategies, a focus on prevention of transmission in addition to preventing disease may help in innovating responses (Burns, Meade and Messionnier 2014). Improving effectiveness at a program level can be achieved by administering more boosters, including in pregnancy, or by al-

tering the vaccines to increase the duration of protection. The latter is not necessarily in the commercial best interests of industry (Burns, Meade and Messionnier 2014), and may require some public stimulus.

Developing a new direction for pertussis vaccines requires innovation at the interface between different disciplines. It takes time for applied problems to be translated into answerable scientific questions. Every three years an international multidisciplinary *Bordetella* Symposium brings together people who work on every aspect of pertussis from immunological studies in animals, through clinicians, to public health practitioners. This is a unique forum in which diverse groups can try to understand each other and share questions and ideas. At the 2004 meeting in Hinxton, Cambridge, UK, the question of studying how to interrupt the transmission of pertussis was raised. Nine years later, at the 2013 meeting in Dublin, Ireland, animal models in mice and baboons were presented that are starting to answer the question (8th International Symposium on Bordetella 2006; 9th International Symposium on Bordetella 2010). It may take time to discover how a better vaccine might be constructed, although science is not a linear process, and progress unpredictable. Developing a new and better vaccine may be expensive, but the costs of managing cases and outbreaks are also high. Outbreaks, disease and death are a burden and an expense borne by public health and the public, while vaccine development costs are borne by the academic sector and industry. A long-term perspective and intersectoral partnership approach combining the perspectives of all disciplines would benefit everyone.

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