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A Critical Evaluation of Whole Cell Pertussis Vaccines on their Composition and Efficacy in Comparison to Acellular Pertussis Vaccines

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Abstract

Diphtheria-Tetanus-Pertussis vaccine has been included in the National Immunization Schedule. DTP vaccines that have been developed can be broadly classified based on the pertussis component i.e. 'The whole cell pertussis vaccine' (wP) and 'The acellular pertussis vaccine' (aP) which contains only specific antigens of Bordetella pertussis. But, mere presence of more or less antigenic components does not determine their efficacy. During the period 1991 to 1996, the western world gradually transitioned from the whole cell pertussis vaccine to the acellular pertussis vaccine. However, there was an increase in cases of pertussis in western countries in the first decade of 21st century, making pertussis the only vaccine preventable disease on rise. The durability of protection with acellular vaccine is not as good as with whole cell vaccine. The acellular pertussis vaccine's failure to deliver durable infection to children had also led to the 2010 California epidemic.The aP vaccine is devoid of crucial antigens participating in the pathogenesis of disease unlike wP vaccine and has slightly lower reactogenicity, thus lower efficacy. Therefore, the duration of protection after immunization by wP vaccine is more as compared to aP vaccine and the average longest protection lasts for about 10-12 years. The wP vaccine also confers cross immunity against B. parapertussis which the aP vaccine does not.

Key words Bordetella pertussis, Whole cell pertussis vaccine, Acellular pertussis vaccine, Pertussis antigens, vaccine efficacy

INTRODUCTION

The Diphtheria-Tetanus-Pertussis [DTP] vaccine forms a very important component of the Universal Program of Immunization and subsequently the Expanded Program of Immunization. It has been included in the National Immunization Schedule of practically all the nations, developed, developing and the underdeveloped, of the globe. This immunization program is carried out through-out the year for decades together. The prevalence of pertussis has diminished worldwide only due to effective implementation of active immunization program. Interestingly, neither natural disease nor vaccination provides complete or lifelong immunity against disease or re-infection.[1,2]

However, there was an increase in cases of pertussis in western countries in the first decade of 21st century, making pertussis the only vaccine preventable disease on rise. Possible explanations for increase in disease incidence include incomplete vaccination, decreased vaccine efficacy, waning immunity, all or any one.[3] Without natural re-infection with B. pertussis or repeated booster vaccinations, adolescents and adults are also susceptible to clinical disease, if exposed.[1,4] Combination vaccines have been developed like the tetravalent (Diptheria Toxoid, Pertussis, Tetanus Toxoid and Haemophilus influenza), pentavalent (Diptheria Toxoid, Pertussis, Tetanus Toxoid, Haemophilusinfluenzae and Hepatitis B) and the hexavalent (Diptheria Toxoid, Pertussis, Tetanus Toxoid, Haemophilus influenza, Hepatitis B and the Inactivated Poliomyelitis) vaccines. These combination vaccines can be broadly classified based on the pertussis component i.e 'whole cell pertussis vaccine' (wP) and 'acellular pertussis vaccine' (aP).

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Antigenic Components of B. pertussis

Bordetella pertussis is a gram negative, pleomorphic bacillus responsible for causing pertussis. It carries multiple antigenic components along with itself to evoke an antigen-antibody response. Four serological types have been separated on culture of which the Phase I is smooth and toxic, whereas Phase IV is rough and nontoxic. There are four major antigenic components in the smooth form in addition to other antigens and toxins.

(i)Agglutinogen is a surface antigen.

(ii)Toxins: These are of 2 types, heat stable and heat labile.

Of the heat stable toxins, pertussis toxin (PT) is an important and major virulence protein. Pertussis toxin has three components: A) Islet activating protein B) Lymphocyte promoting factor C) Histamine sensitizing factor. This PT, expressed on the surface of bacillus, on treatment with formalin loses its biological activity but retains its antigenicity. The second heat stable toxin, lipopolysaccharide toxin (LPST), is an endotoxin which is non-protective in nature but in serum, in conjugation with compliments has bactericidal activity.

The heat labile toxin (HLT) is a cytoplasmic protein in bacteria. It does not produce any antibodies in humans. The tracheal cytotoxin (TC) is another toxin which produces ciliastasis of ciliated columnar epithelium causing accumulation of secretions and obstruction of air passages by mucous plugs leading to spasmodic cough.

(iii)Haemagglutinins (HA): There are three types of HA: A) Filamentous Haemagglutinin (FHA) from surfaced fimbriae comprising the fibrillar protein, antibody to which confers local or respiratory tract immunity B) Pertussis Toxin Haemagglutinin (PTHA), which minimizes the colonization scope. These 2 HAs augment adherence of H. influaezae, Streptococcus and D. pneumonia. C) Lipid Factor (LF).

(iv)Adenylate Cyclase (AC): This is activated by calmodulin which is intracellular. Of the two known ACs, only one has ability to enter the target cells and act as a toxin. AC

inhibits chemotaxis and phagocytosis.

(v)Pertactin (PRN) is an outer membrane protein.

(vi)Dermonecrotic toxin causes shedding of ciliated epithelium.

(vii)Fimbriae (FIM) that mediates attachment of the bacillus.

Composition of DTP Vaccines:

Two types of pertussis vaccines are available in the market, wP and aP vaccines. wP is a whole cell pertussis vaccine derived from standardized culture of a specific strain of the bacteria and contains complete, heat killed and formalin treated cell of B. pertussis and thus has all the antigenic components present on the cell wall, fimbriae and inside the cell. Contrary to this, aP vaccines contain only specific antigens instead of all the antigens. Thus, there are different types of acellular pertussis vaccines depending upon the number of antigens contained. They are single component (PT), dual component (PT and FHA), triple component (PT, FHA and PRN) and penta component (PT, FHA, PRN and fimbriae 2 and 3).[5] Therefore, wP vaccine, which includes all the antigens of bacillus, generates a robust immunogenicity leading to better immune protection against all the antigens of bacillus.

Efficacy and/or Immunogenicity of Pertussis Vaccines:

The role in vaccine efficacy or the effectiveness of varying amounts of biologically active PT, LPST, TC and AC is unclear.[6] Tests applied to check the efficacy of wP differ from the tests applied to aP. This has led to a debate on whether antibody levels in these different types of vaccines closely correlate with protective efficacy against pertussis.[7] The protective efficacy of wP has been proven by observing -

(i)Reduction in disease burden,

(ii)Resurgence of disease with decline in vaccine coverage,

(iii)Relationship between attack rate during outbreaks and proportion of immunized population, and

(iv)Evidence that may suggest herd immunity,[5]

Although, it is impractical to calculate efficacy of pertussis vaccine across various studies, reiterating that all wP and aP vaccines are not equivalent to each other, it is considered that the range of efficacy is 85-95% for wP vaccine and 75-90% for aP vaccine. Differences in efficacy among various aP depend on overall impact of the number of antigenic components, their concentrations and manufacturing process. Thus, mere presence

Table 1 – a comparative overview of vaccine efficacy of DTw Pan dvarious DTaP

Mfg = Manufacturer, CI = Confidence Interval, Eff– Efficacy, A = Amvax, B = Behringwreke, C = Connaught, LT = Lederle Takeda, PM = Past eur Merieux, SKB = Smith Kline and Beecham

Components	**DTaP Single Component (PT)**		**DTaP Dual Component (PT, FHA)**		**DTaP Triple Component (PT, FHA, PRN)**		**DTaP Penta Component (PT, FHA, PRN, FIM 2 & 3)**		**Whole Cell Vaccine**	
	Mfg	**Eff. 95%CI**	**Mfg**	**Eff. 95%CI**	**Mfg**	**Eff. 95%CI**	**Mfg**	**Eff. 95%CI**	**Mfg**	**Eff. 95%CI**
	A	71% (63-78)	PM	86% (71-93)	SKB	84% (76-90)	C	85% (81-89)	PM	96% (87-94)
			SKB	59% (51-66)	SKB	89% (77-95)	LT	82% (73-87)	B	97% (83-100)
									B	97% (79-100)
									LT	91% (85-95)
Interpretation of efficacy	--		Least efficacious		Moderately efficacious		Moderately efficacious		Highly efficacious	

of more or less components does not determine their efficacy. Currently available aP vaccines are all deemed to be efficacious.[7] A randomized controlled trial of 2, 3 and 5 component aP vaccine with wP vaccine concluded that both the vaccines (wP and aP) had similar efficacies against culture proven pertussis.[8]

The efficacies of aP and wP depend upon the case definition of pertussis as defined by WHO. However, the best aP vaccines have higher efficacy than the low efficacy wP vaccines but they may be less efficacious than the highest efficacy wP vaccines in preventing whooping cough.[9-12] Table 1 shows a comparative overview of efficacy of wP and various aP.

Table 2 – Estimated duration of protection against pertussis after primary schedule of vaccination (3 doses)

Year	Type of Vaccine	Type o f Study	Duration of imm unity in years
1993	DT wP	Surve illanc e	8
1996	DT wP	Surve illanc e	5-10
1999	DT wP	Surve illanc e	5-14
2001	DT aP	Cohort Study	6
2002	DT aP	Cohort Study	6
2003	DT aP	Surve illanc e	6-9
2006	DT aP	Vac cine S tudy	6

DISCUSSION

Pertussis is a common cause of prolonged cough illness. An American study showed that 26% of university students with cough ≥6 days had pertussis infection.[13] Most of the cases go unrecognized and untreated facilitating the spread of disease in the community and older people are the most important source of transmission.[6,14] Nearly 26,000 cases were reported in 2004 in US, the highest since 1959. Amongst the unimmunized subjects, about 1% of adolescents and young adults are infected annually, and only about 1 in 6 is symptomatic i.e. for every classical case of clinical pertussis, there are 5 asymptomatic or clinically insignificant infected subjects.[15] After the implementation of Universal Immunization Program in 1940s, there was a sharp decline in number of pertussis cases. During the period 1991 to 1996, the Western world gradually transitioned from whole cell pertussis vaccine to less reactogenic acellular pertussis vaccine.[16] Between 1980 and 2004, there was a dramatic increase in pertussis cases in the Western countries including Netherlands, Canada and USA, making it only vaccine preventable disease on the rise.[3] This resurgence was partly contributed to the use of Polymerase Chain Reaction [PCR] technique and other serological methods like detecting the levels of IgG against purified pertussis toxin and the IgA levels against crude cell wall protein, for diagnosis of the disease, better surveillance and patient awareness.[3] It was also partly attributed to the changes in genomic sequences of bacterial PRN and PT.

In late 1990's, there was sudden resurgence in the pertussis cases reported in Canada. It was found that infants had 2.7 fold increased incidence of the disease in comparison to 9-15 fold increase in children between 1 and 19 years, and 22.5 fold increased incidence in adults. Pertussis affected predominantly children who were immunized with a vaccine introduced in the mid-1980s. Evolution of the age distribution of cases paralleled the aging of this cohort with a slow but steady drift of disease from early childhood to adolescence. The sudden increase in pertussis cases in Canada was largely attributed to a cohort effect resulting from poorly protective pertussis vaccines used between 1985 and 1998.[17] Similarly, rise in the number of cases reported for pertussis was also seen in Netherlands in older children.

A number of causes were studied to find the exact reason for increased incidence of the disease including surveillance, vaccine quality, and others. It seemed to reflect a true increase in incidence of the disease. Though, the exact cause was not determined, a possible mismatch between the vaccine and circulating Bordetella strain was being investigated.[18] However, the concerns that the efficacy of current pertussis vaccines may have been lost to this antigenic drift have not been substantiated.[19] Waning immunity of acellular pertussis vaccines was also equally important.

During the 2010 California pertussis outbreak, in a study 904 cases of pertussis were identified amongst 263,496 persons from the age group 8-20 years. It was found that people who were inoculated, solely, with 5 doses of aP vaccines, were at a higher risk of contracting pertussis than those who had received at least 1 or more wP vaccine. This risk was reduced, but not eliminated, when adolescents received a sixth booster dose of Tdap. A trend towards higher rates of pertussis among children who had never received prior wP vaccine was also noted. The researchers also found that receipt of 1 or more wP vaccines markedly augmented the durability of immunity from subsequent aP vaccines. They inferred that a wholly aP vaccine series is significantly less effective and durable than the one that contains traditional wP vaccine.[20]

aP was introduced in 1991 and wP was retired from the use in United States in 2001. The studied subjects were old enough to have received wP vaccine and young enough to have received aP vaccine. All children born after 2001 would have had only aP vaccine, whereas those born in the preceding 10 years may have had some combination of 2 vaccine types. It was also notable that the attack rate of pertussis during the outbreak in California in 2010 was markedly less in adolescents, whether or not they had received the Tdap booster. The results confirmed a profoundly enhanced protection from pertussis for all persons who had ever received a dose of wP vaccine, when contrasted with those who had received only aP. This effect persisted for years, demonstrated by an enhanced effectiveness of Tdap in those who had received wP vaccine as a part of their primary series of pertussis vaccination. Though, the study had its own limitations e.g. it was a retrospective study, pertussis testing was at the discretion of the clinician, permitting some degree of selection bias, and PCR testing was not confirmed by concomitant bacterial culture. Also, subjects included were in larger age difference and the age adjustment was not possible. It is also worth noting that the vaccine schedule for aP was adapted to that of the traditional wP schedule, but had not been studied for the complete 5-dose series.[20]

Also, pertussis cases were seen in young children and the elder children had received wP vaccines. Thus, this comparison of wP vaccinated individuals versus the aP vaccinated individuals was really a comparison of pertussis in adolescents receiving wP

vaccines versus the young children receiving aP vaccines.

In another study, during the same period, where 138 PCR positive cases of pertussis were compared with 899 PCR negative and more than 54,000 Kaiser Permanente Northern California matched controls, it was reported that, teens whose first four DPT shots contained aP, were six times more likely to be pertussis PCR-positive than those whose initial 4 shots contained wP. Children vaccinated with aP were also four times more likely to get the disease than who were vaccinated with a mixture of both aP and wP. The risk of pertussis increased by an average of 40% with each additional dose of aP when compared to 4 doses of wP. Those who had not received Tdap booster had nearly 10-fold higher risk associated with having received 4 aP versus 4 wP doses. This is probably due to the reason that those with wP history had higher titres to PT, indicating that wP induced better B-cell memory priming. The results also indicated that a booster dose of Tdap does not overcome the advantage in protection from pertussis afforded to those who previously received 4 doses of wP. Despite this, boosting the newly emerging cohort of aP-only teenagers with Tdap remains the best means currently available to help protect this group against disease.[21]

The aP vaccine's failure to deliver durable protection to children had led to the 2010 California epidemic. Protection from childhood immunization (and natural infections) is thought to wane after 4 to 12 years.[22] The estimated duration of protection after the primary schedule of vaccination (3 doses) is summarized in the Table 2.[23] Data from the 2010 California outbreak suggest that the duration of protection may be even shorter.[24] In California alone there were 9,154 cases including 10 deaths.[25] This was the highest number of reported cases since 1947.[26]

The durability of protection with aP vaccine is not as good as with wP vaccine. An analysis of the time elapsed following fifth dose relative to when pertussis infection occurred showed that after 5 years, vaccine efficacy was 71% below where it stood immediately after the fifth dose. This translated into a 15 fold higher relative risk for infection in children during the sixth year following their final dose, compared with their first 12 months after their fifth dose.[23] Each year elapsing after the final dose of aP vaccine is associated with 36% increased risk of contracting pertussis.[27] This later led to the approval of use of Tdap vaccine for adolescent and adults in 2005, and caused steady decline in overall cases of the pertussis. Thus in 2006, booster dose of Tdap was recommended to all adolescents and adults in United States.[28,29]

Clinical trial on wP vaccine conducted during an epidemic of pertussis in the Faroe Island has demonstrated that wP vaccine provided protection against clinical whooping cough in immunized individuals and also ameliorated the severity of disease in immunized persons. In a study in US, single dose of wP provided an efficacy of 44% and 4 doses of the same showed an estimated efficacy of 80% against paroxysmal cough.[30] A similar study in Denmark showed 36% efficacy of single dose of wP in preventing hospitalization and upto 86% efficacy after 3 doses.[10] Various trials of aP vaccines incorporated wP as controls. The data available from these prove the wP efficacy. The Mainz, Munich and the Senegal trial reported the efficacy of wP at 98%, 96% and 96% respectively.[10,18,31] A systemic review of 3 large, randomized double blind, controlled trials of aP vaccine concluded that multi component aP vaccines have better absolute efficacy compared to 1 and 2 component aP vaccines.[32,33]

A Cochrane review tested the effects of aP vaccines in 45 safety and 6 efficacy randomized controlled clinical trials. Results of the efficacy trials demonstrated significant differences in the efficacy (91-96% in wP versus 82-85% in aP vaccines). However, risk of death due to any cause and death due to infection did not differ significantly. Little is known about efficacy of wP in older age groups. Also, the reactogenecity of wP was thought to be too high to permit its use in older children, adolescents and adults.[7]

aP vaccines were expected to reduce the incidence of major adverse effects following immunization [AEFI] of wP. In practice, it has been noted that aP has succeeded in the same. The rate of anaphylaxis with wP is around 2/100,000 and that of seizures is 1/1750, whereas that of aP is much below that. wP also has some other drawbacks. The rate of inconsolable cry 3 hours after vaccination, is 1/100 and the incidence of fever >40.5O was about 0.3% with wP vaccines. The other common local and generalized reactions with wP include redness, induration, oedema, local tenderness, drowsiness and anorexia. These are also seen with aP, but with lesser severity and these mostly subside spontaneously. The adverse effects following immunization fell with successive doses of wP and aP vaccines. The incidence of fever, redness and swelling remained fairly constant with wP vaccines. The frequency of AEFI following primary aP vaccination did not differ from that observed in control group, regardless of the number of vaccine components included.[32] However, after the primary series of immunization, the rate and severity of local reactions tend to increase with each successive aP vaccine dose in older children and adolescents. To reduce the reactogenicity of booster injections, aP vaccines with reduced concentrations of the antigen have been formulated for use in adolescents and adults. As local reactions increase with age and numbers of injections, wP-containing vaccines are not recommended for use in adolescents and adults.[7] A Cochrane review in 2009 found that use of combined vaccines did not result in significant increase in the incidence of serious adverse events but may cause more frequent minor reactions.[34]

The effects of withdrawal of pertussis immunization have confirmed the effectiveness of wP vaccines. Documented pertussis rate in vaccinated and unvaccinated communities is also an indication of wP vaccine efficacy. The national surveillance in US has demonstrated more than 95% reduction in pertussis. The surveillance data from 1992 to 1994 found an overall wP efficacy of 82% after four or more doses.[35] wP vaccine also provides sustainable herd immunity post vaccination thus reducing the disease burden.[36,37]

aP vaccines have few of their own limitations too. It is devoid of some crucial antigens participating in the pathogenesis of the disease. The aP vaccines do not contain all the antigenic components like wP vaccine and thus providing incomplete or limited immunity. Also, as the pertussis components are different for different aP vaccines, they cannot be used interchangeably.[38] One needs to stick to the same brand preferably. This can pose a problem during booster vaccination wherein the availability of aP vaccine is constrained. aP also reduces the anti-PRP Hib antibody titres over a period of time.[39-41]

The cost of vaccination is also a major cause of concern in developing and underdeveloped world where incidence of the disease is thought to be high. aP vaccines are much costlier than wP vaccines due to high production costs and development costs, having a huge impact on the overall national health budget. Many health economists have already expressed their concern over this.

This cost factor also pose constrains from inclusion of aP vaccine by replacing wP vaccine in the national immunization schedule in developing and underdeveloped nations.[7]

CONCLUSIONS

1. The pathogenesis of Pertussis disease is not a result of a single or a few antigens of B. pertussis, but is a collective effect of all the antigens which augment each other's effect.
2. The wP vaccines have all the components of the bacilli, thus inducing complete immunity against all the antigens. Contrary to this, the aP vaccines have 2, 3 or 5 antigenic components thus fail to give immunity comparable to wP.
3. To get a robust immunity from aP vaccines, patient has to receive the vaccine with 3 or more component acellular vaccine and has to look for similar component vaccines.
4. Though, switching of the components does not create a major hindrance in the reactogenecity of the vaccine administered initially, insufficient data exist on safety, immunogenicity and efficacy of different aP vaccines when administered interchangeably. However, the wP vaccines can be used interchangeably, if developed in accordance to the WHO set of quality requirements for production and release of wP vaccines.
5. Duration of protection after immunization by wP vaccine is much more as compared to aP vaccine and the average longest protection lasts for about 10-12 years.
6. wP vaccines have been proved to confer herd immunity against pertussis, which helps in prevention of outbreak of an epidemic of pertussis.
7. The immunity induced by aP vaccine wanes off over a period of time after the second booster as compared to that of wP vaccine. This can lead to outbreak of an epidemic like situation (resurgence) in the adolescent and the adult age group over a span of time as was seen in California in 2010.
8. wP vaccines also confer cross immunity against B. parapertussis but aP vaccines do not.
9. The AEFI of both the vaccines are nearly equal as for the major AEFI; however, aP vaccine reduces the minor AEFI markedly.
10. The aP vaccine interferes with the immune response evoked by other conjugates of a combination vaccine, giving slightly lower antibody titres.
11. The cost of aP vaccine is a major setback for its implementation in national immunization schedule.
12. wP vaccines have a higher reactogenecity in older children, adolescents and adults, thus, limiting its use in them.
13. Pertussis components in adolescents and adults have a higher reactogenecity, therefore, a booster dose of acellular pertussis with lesser pertussis component concentration needs to be used in adolescent and adults.

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