Advances in Bioscience and Bioengineering
2019; 7(1): 8-12
http://www.sciencepublishinggroup.com/j/abb
doi: 10.11648/j.abb.20190701.12
ISSN: 2330-4154 (Print); ISSN: 2330-4162 (Online)

Review Article

History and Prospect of Vaccines Against Pertussis

Kaminaka Kazuyoshi[1], Chikateru Nozaki[2, *]

[1]Development Department, KM Biologics Co., Ltd., Kumamoto, Japan

[2]Department of Medical Technology, Kumamoto Health Science University, Kumamoto, Japan

Email address:
nozaki@kumamoto-hsu.ac.jp (C. Nozaki)

[*]Corresponding author

To cite this article:
Kaminaka Kazuyoshi, Chikateru Nozaki. History and Prospect of Vaccines Against Pertussis. *Advances in Bioscience and Bioengineering*. Vol. 7, No. 1, 2019, pp. 8-12. doi: 10.11648/j.abb.20190701.12

Received: June 9, 2019; **Accepted**: July 4, 2019; **Published**: July 16, 2019

Abstract: Pertussis, known as whooping cough, is a severe respiratory disease most commonly caused by the bacterium *Bordetella pertussis*. It is transmitted from person to person by aerosols and infects the ciliated epithelium of the airways. Pertussis was responsible for high mortality rates before the introduction of effective vaccines in the second half of the 20th century. Vaccination is thought to be the most effective method for control pertussis. There have been two types of pertussis vaccines available. The first-generation vaccine was the whole-cell vaccine, which was efficacious. However, it caused occasional side effects. The whole-cell vaccine was gradually replaced by the acellular vaccine. The acellular vaccine consists of detoxified, purified pertussis antigens. Despite the widespread use of the acellular vaccine, pertussis has recently been on the rise. In order to overcome such a situation, developments of new pertussis vaccines are in progress over the world. One is a genetically modified live vaccine which is thought to maintain safety while inducing immunity close to natural infection. And also there are a mucosal vaccine using lactic acid bacteria carrying components of pertussis and a bacterium-like particle vaccine with components of pertussis. In this review we introduce history and prospect of vaccines against pertussis.

Keywords: Pertussis, Whole-Cell Vaccine, Acellular Vaccine, Live Attenuated Vaccine, *Lactococcus lactis*, Bacterium-like Particle

1. Introduction

Pertussis is a severe respiratory disease in infants, young children and even in adults [1-6]. It is classically known as whooping cough because of its characteristic cough. It is most caused by the bacterium *Bordetella pertussis* (*B. pertussis*). The typical presentation of pertussis is seen in unimmunized children (less frequently in adolescents and adults) and is a three-stage illness: catarrhal, paroxysmal, and convalescent.

The duration of illness is typically 6 to 12 weeks but sometimes longer. Symptoms develop after an average incubation period of 7 to 10 days (range, 5 to 28 days). The catarrhal phase of disease is a nonspecific, mild clinical syndrome which lasts from 1 to 2 weeks. Nasal congestion, rhinorrhea, lacrimation with conjunctival injection, malaise, mild sore throat, and mild cough similar to a common cold are seen. It is then followed by worsening cough, and the paroxysmal stage begins.

The paroxysmal phase usually lasts 2 to 6 weeks. The paroxysms are repetitive series of 5 to10 or more forceful coughs during a single expiration, followed by a sudden inspiratory effort leading to the characteristic whoop. Posttussive vomiting is a common phenomenon. Between attacks, the patient appears relatively well. As the illness progresses, episodes of cough paroxysms usually increase in frequency and severity, particularly at night.

The convalescent stage, which usually lasts 1 to 12 weeks, is characterized by a decreasing frequency and severity of coughing episodes, whooping, and vomiting. During the recovery period, superimposed viral respiratory infections can trigger a recurrence of paroxysms. Patients with classic pertussis caused by primary infection have leukocytosis associated with lymphocytosis.

Pertussis was responsible for high mortality rates before the introduction of effective vaccines in the second half of the 20th century. Pertussis is the prevalent vaccine-preventable

disease in the developed world. Two types of pertussis vaccines are currently available, the first-generation whole-cell vaccine and the more recent acellular vaccine. Thanks to a substantially improved safety profile and high efficacy, the acellular vaccine has replaced the whole-cell vaccines in many parts of the world. However, pertussis is now increasing even in countries with high vaccine coverage.

2. *Bordetella Pertussis*

B. pertussis is a small gram-negative bacterium [7-9]. It secrets pertussis toxin (PT) which is a multisubunit (AB_5) protein toxin consisting of an enzymatically active A subunit (S1) non-covalently associated with a pentamer of binding (B) subunits (S2, S3, 2 copies of S4 and S5). PT is a critical factor related to mortality in young infants and is unique to *B. pertussis*. PT is responsible for leukocytosis with lymphocytosis seen in *B. pertussis* infections in unimmunized individuals. Leukocytosis is a major risk factor for severe disease in unprotected infants. PT in detoxified form is a component of all acellular vaccines.

B.pertussis has a number of adhesins that anchor it to the epithelial lining of the host respiratory tract. Pertactin (PRN) is a 69-kDa membrane protein to play a role in attachment as it contains the RGD tripeptide that is common in other bacterial adhesins. It is a potent immunogen, known to be a primary target for pertussis-specific T-cells. PRN is almost completely homogeneous across all strains. Some acellular vaccines containing PRN are shown to be more effective than vaccines without PRN. Anti-PRN antibodies appear to help phagocytosis of *B. pertussis* by host immune cells.

Fimbriae are surface proteins of *B.pertussis* and are important antigens in the pathogenesis of pertussis, functioning as adhesins. They are built up by subunits to make long filamentous structures on the surface of the bacteria. *B.pertussis* possesses two serotypes fimbriae which are composed of either the Fim2 or Fim3 major subunits (22.5 and 22.0 kDa, respectively). Fimbriae mediate the adherence of the microorganism to the epithelium of the respiratory tract and elicit a protective immunogenic response. Fimbriae could be advantageous of for the creation of an acellular vaccine against pertussis.

Filamentous hemagglutinin (FHA) is a 220-kDa outer membrane protein. It is one of the earliest proteins expressed, detectable within a few minutes of infection, and in known to have many functions. FHA-deficient mutants cannot adhere to host cells in vivo or in vitro. FHA binds to receptor type 3 on the surface of host macrophages, which leads to a delayed T-cell response in mouse models. It suppresses the Th1 cell-mediated response, which lowers host immunity.

3. Whole-Cell Vaccine

The whole-cell vaccine was developed during the early 1900s using dead cells of *B. pertussis* [10-12]. It became prevalent in many developed nations during the 1940s and 1950s and effectively brought the disease under control. When it first came into use, the vaccine was delivered 3 times throughout early childhood. Because localized reactions tend to increase with age, as the immune system increases in strength, this vaccine is not approved for adolescents or adults.

The vaccine is based on standardized strains of *B.pertussis* that are killed and often treated with formalin; however, the exact method of production varies among manufacturers. Each vaccine undergoes rigorous testing that assesses potency, toxicity, sterility, and bacterial concentration. Alum adjuvants are always added to the whole-cell vaccine. Thiomersal and other preservatives may also be present in the vaccine. Commonly, the vaccine is paired with diphtheria and tetanus toxoids to form a combined vaccine (DTwP). This vaccine elicits a strong immune response that often leads to adverse reactions.

Immunization with the whole-cell vaccine is effective and the vaccine is relatively inexpensive. However, immunization with the whole-cell can cause severe neurologic disorders and minor side effects, such as anorexia, drowsiness, fever, irritability, prolonged crying, vomiting and pain/redness/swelling/hardening at the injection site. The acellular vaccine has been developed in the hope that it would be as effective but safer than the whole-cell vaccines.

4. Acellular Vaccine

Currently, the preferred vaccine in most industrialized nations is the acellular vaccine [13-18]. The acellular vaccine is created using antigen proteins identified and isolated from a pathogen. In order for the acellular vaccine to be effective, it must provide an immune response similar to that triggered by direct contact with the pathogen itself.

The earliest form of this vaccine was created in 1981 by a Japanese researcher. The current acellular vaccine is made up of 5 different antigens: PT, FHA, PRN, and fimbriae. Animal models and human clinical trials were used to assess which virulence factors produce protective antigens upon exposure. The vaccine differs significantly from one manufacturer to the next, as there are no standardized strains from which these antigens are purified from, and no standardization for the processes of purification, detoxification, or incorporation of adjuvants and preservatives.

The components of the acellular vaccine are combined with diphtheria and tetanus toxoids (DTaP). This vaccine is usually administered 5 times during childhood and once more during early adolescence. In order to combat the increased strength and consequently reaction of an older immune system, the "boosters" after the original inoculation contain lower concentrations of the antigens, in order to minimize their reactogenicity. The DTaP vaccine has been successful because it effectively minimizes the adverse side effects so prevalent in the DTwP vaccine. Despite the widespread use of the acellular vaccine, pertussis has recently been on the rise.

5. Live Attenuated Vaccine

Natural infection with *B.pertussis* has long been considered to induce strong and long-lasting immunity that wanes later

than vaccine-induced immunity [19, 20]. Therefore, live vaccines could be possible to mimic as closely as natural infection. Mielcarek et al. developed such a live vaccine candidate [21-23]. They constructed attenuated live vaccine BPZE1 by removing or altering genes that are involved in the pathogenesis of pertussis. Three virulence factors were genetically targeted: tracheal cytotoxin, pertussis toxin, and dermonecrotic toxin.

BPZE1 was found to induce protection in infant mice after a single intranasal administration that is superior to the protection provided by the current acellular vaccine. BPZE1 provided protection against infection with *B.pertussis*, which was not seen after vaccination with acellular vaccine. BPZE1 has completed a first-in-man phase I trial and was shown to be safe in young male volunteers, able to transiently colonize the naso-pharynx and to induce antibody responses to *B.pertussis* antigens [24]. Advantages of the use of BPZE1 include the relatively low production costs, making it especially attractive for developing countries, its needle-free, easy, and safe mode of administration, and its potential to induce mucosal immunity in addition to systemic immunity. This vaccine candidate may therefore be useful for long-term control of pertussis.

6. Mucosal Vaccine Using *Lactococcus Lactis*

B.pertussis enters and colonizes the body through the respiratory mucosa which is the first line of the host defense against this pathogenic organism. Several studies have suggested the importance of local secretory antibodies (IgA) and Th1-type immune responses to protect *B.pertussis* [25-27].

Mucosally-administered vaccines can induce both the systemic and the mucosal immune responses while parenteral vaccines mainly activate the systemic immune response. Due to the fact that mucosally-administered soluble antigens are in general poorly immunogenic, several approaches, such as their encapsulation or expression in attenuated bacterial hosts, have been used to improve their immunogenicity. However, the attenuated bacterial hosts may still be able to cause a limited infection in infants as well as the aged and immunocompromised people [28]. An attractive alternative to overcome this problem is the development of a new vaccine in association with lactic acid bacteria which are safe mucosal delivery vehicles [29].

For development of a simplified, cost-effective and well-defined vaccine candidate against *B.pertussis*, Torkashvand et al. constructed a food-grade expression system harboring a F1S1 fusion protein of *B. pertussis* to be produced in *Lactococcus lactis* (*L. lactis*) NZ3900 as a new oral vaccine model against whooping cough, caused by *B. pertussis*. F1S1 was composed of N-terminally truncated S1 subunit of pertussis toxin and type I immunodominant domain of filamentous hemagglutinin which are both known as protective immunogens against pertussis.

The recombinant *L. lactis* was administered via oral or intranasal routes to BALB/c mice and the related specific systemic and mucosal immune responses were then evaluated. The results indicated significantly higher levels of specific IgA in the lung extracts and IgG in sera of mucosally-immunized mice, compared to their controls. It was revealed that higher levels of IgG2a, compared to IgG1, were produced in all mucosally-immunized mice. Moreover, immunized mice developed Th1 responses with high levels of IFN-γ production by the spleen cells. These findings provide evidence for *L. lactis* to be used as a suitable vehicle for expression and delivery of F1S1 fusion protein to mucosa and induction of appropriate systemic and mucosal immune responses against *B.pertussis*.

7. Bacterium-like Particle Vaccine

As mentioned before, the pathologic and immune reactions against *B.pertussis* begin with the colonization of *B.pertussis*. In order to overcome this disease, it is essential to prevent the initial adherence and colonization of the bacteria. As most purified protein antigens are poorly immunogenic, appropriate delivery systems or adjuvants are needed to enhance immune responses. The traditional alum adjuvants encourage production of antibodies (Th2 response). However, it is known that Th1 response is a vital component of pertussis protection.

A variety of adjuvants have been used to enhance the mucosal immune response to pertussis antigens [30, 31]. A novel adjuvant system of bacterium-like particles (BLPs) was developed based on food grade bacteria, and it has shown promise for use in mucosal vaccines [32]. BLPs are produced by pretreatment in hot acid which destroys all of the intracellular components, membrane structure and cell-wall components. The treated bacteria become non-living particles. The capacity to induce maturation and activation of antigen-presenting cells renders BLPs suitable for delivery of the associated antigen for presentation in the context of MHC class I and/or MHC class II [33, 34]. As a mucosal adjuvant system, the efficacy of BLPs has been shown previously against malaria parasites, Yersinia pestis and pneumococcus [35]. The potent adjuvant activity mediated by BLPs has been observed, even when simply mixed with the subunit antigens [36-38].

Shi et al. reported that bacterium-like particles (BLPs) were adopted as a mucosal adjuvant for an intranasal pertussis vaccine and evaluated on the ability to induce serum and mucosal antibodies as well as potency against intranasal challenge in mice. Groups with or without aluminum adjuvant were also evaluated through both intranasal and intraperitoneal inoculations. Vaccination with BLPs via the intranasal route led to rapid IgG and IgA production and provided strong protection against inflammation induced by infection. The results support an intranasal pertussis vaccine with BLPs adjuvant as a promising candidate to elicit protective immunity against pertussis.

8. Conclusion

Pertussis is a severe respiratory disease caused by *B.pertussis*. The first vaccine against pertussis was the whole-cell vaccine. However, it was replaced by the acellular vaccine because the whole-cell vaccine caused side effects. Though the acellular vaccine has been widely used in the world, pertussis has been not eradicated and tends to increase gradually. In order to overcome such a situation, new vaccines have been developed. One is a genetically modified live vaccine which is thought to maintain safety while inducing immunity close to natural infection. In addition, there are a mucosal vaccine using lactic acid bacteria carrying components of pertussis and a bacterium-like particle vaccine with components of pertussis to enhance the immunogenicity. These new vaccines would be expected to control pertussis.

References

[1] Kilgore PE, Salim AM, Zervos MJ, Schmitt HJ. Pertussis: Microbiology, Disease, Treatment, and Prevention. Clin Microbiol Rev. 2016 29 (3): 449-86.

[2] G. Fedele, P. Stefanelli, Pertussis in infants and the resurgence of a vaccine preventable disease: what to do? Commentary, Ann. Istituto. Super. Sanita 53 (2) (2017 Apr-Jun) 100–103.

[3] Mattoo S, Cherry JD. Molecular pathogenesis, epidemiology, and clinical manifestations of respiratory infections due to Bordetella pertussis and other Bordetella subspecies. Clin Microbiol Rev. 2005; 18 (2): 326–382.

[4] Pertussis vaccines: WHO position paper - September 2015. Wkly Epidemiol Rec. 2015; 90 (35): 433–458.

[5] Falleiros Arlant LH, de Colsa A, Flores D, Brea J, Avila Aguero ML, Hozbor DF. Pertussis in Latin America: epidemiology and control strategies. Expert Rev Anti Infect Ther. 2014; 12 (10): 1265–1275.

[6] Mazzilli S, Tavoschi L, Lopalco PL. Tdap vaccination during pregnancy to protect newborns from pertussis infection. Ann Ig. 2018 Jul-Aug; 30 (4): 346-363.

[7] Delma J. Nieves, Ulrich Heininger. 2016. *Bordetella pertussis*. Microbiol Spectr. 2016 Jun; 4 (3).

[8] Versteegh F, Schellekens J, Fleer A, Roord J. Pertussis: a concise historical review including diagnosis, incidence, clinical manifestations and the role of treatment and vaccination in management. Rev Med Microbiol 2005; 16: 79–89. [Google Scholar].

[9] Mattoo S, Cherry JD. Review Molecular pathogenesis, epidemiology, and clinical manifestations of respiratory infections due to Bordetella pertussis and other Bordetella subspecies. Clin Microbiol Rev. 2005 Apr; 18 (2): 326-82.

[10] Trollfors B. Bordetella pertussis whole cell vaccines--efficacy and toxicity. Acta Paediatr Scand. 1984 Jul; 73 (4): 417-25.

[11] Edwards KM1, Karzon DT. Pertussis vaccines. Pediatr Clin North Am. 1990 Jun; 37 (3): 549-66.

[12] Wintermeyer SM1, Nahata MC, Kyllonen KS. Whole-cell and acellular pertussis vaccines. Ann Pharmacother. 1994 Jul-Aug; 28 (7-8): 925-39.

[13] Sato Y, Sato H. Development of acellular pertussis vaccines. Biologicals. 1999 Jun; 27 (2): 61-9.

[14] Campins-Martí M1, Moraga-Llop FA. Acellular pertussis vaccines for use among infants and young children. Expert Opin Pharmacother. 2004 Apr; 5 (4): 807-17.

[15] Bailey J. Acellular vaccines for preventing pertussis in children. Am Fam Physician. 2011 Sep 1; 84 (5): 504.

[16] Brummelman J, Wilk MM, Han WG, van Els CA, Mills KH. Roads to the development of improved pertussis vaccines paved by immunology. Pathog Dis. 2015 Nov; 73 (8).

[17] Mazzilli S, Tavoschi L, Lopalco PL. Tdap vaccination during pregnancy to protect newborns from pertussis infection. Ann Ig. 2018 Jul-Aug; 30 (4): 346-363.

[18] Patterson J, Kagina BM, Gold M, Hussey GD, Muloiwa R. Comparison of adverse events following immunisation with acellular and whole-cell pertussis vaccines: A systematic review. Vaccine. 2018 Sep 25; 36 (40): 6007-6016.

[19] von König CH, Halperin S, Riffelmann M, Guiso N. (2002) Pertussis of adults and infants. Lancet Infect Dis 2: 744–750.

[20] Wirsing von König CH, Postels-Multani S, Bock HL, Schmitt HJ (1995) Pertussis in adults: Frequency of transmission after household exposure. Lancet 346: 1326–1329.

[21] Mielcarek N, Debrie AS, Raze D, Bertout J, Rouanet C, et al. (2006) Live attenuated B. pertussis as a single-dose nasal vaccine against whooping cough. PLoS Pathog 2: e65.

[22] Feunou PF, Kammoun H, Debrie AS, Mielcarek N, Locht C. Long-term immunity against pertussis induced by a single nasal administration of live attenuated B. pertussis. Vaccine. 2010 Oct 8; 28 (43): 7047-53.

[23] Li R, Lim A, Alonso S. Attenuated Bordetella pertussis BPZE1 as a live vehicle for heterologous vaccine antigens delivery through the nasal route. Bioeng Bugs. 2011 Nov-Dec; 2 (6): 315-9.

[24] Thorstensson R, Trollfors B, Al-Tawil N, Jahnmatz M, Bergström J, Ljungman M, Törner A, Wehlin L, Van Broekhoven A, Bosman F, Debrie AS, Mielcarek N, Locht C. A phase I clinical study of a live attenuated Bordetella pertussis vaccine--BPZE1; a single centre, double-blind, placebo-controlled, dose-escalating study of BPZE1 given intranasally to healthy adult male volunteers. PLoS One. 2014 Jan 8; 9 (1): e83449.

[25] Higgs R, Higgins SC, Ross PJ, Mills KH. Immunity to the respiratory pathogen Bordetella pertussis. Mucosal Immunol. 5 (5) (2012 Sep) 485–500.

[26] Ross PJ, Sutton CE, Higgins S, Allen AC, Walsh K, Misiak A, Lavelle EC, McLoughlin RM, Mills KH. Relative contribution of Th1 and Th17 cells in adaptive immunity to Bordetella pertussis: towards the rational design of an improved acellular pertussis vaccine, PLoS Pathog. 9 (4) (2013) e1003264.

[27] Hellwig SM, van Spriel AB, Schellekens JF, Mooi FR, van de Winkel JG. Immunoglobulin A-mediated protection against Bordetella pertussis infection. Infect. Immun. 69 (8) (2001 Aug) 4846–4850 PubMed PMID: 11447159.

[28] Bermúdez-Humarán LG. Lactococcus lactis as a live vector for mucosal delivery of therapeutic proteins. Hum. Vaccine 5 (4) (2009 Apr) 264–267.

[29] Pontes DS, de Azevedo MS, Chatel JM, Langella P, Azevedo V, Miyoshi A. Lactococcus lactis as a live vector: heterologous protein production and DNA delivery systems. Protein Expr. Purif. 79 (2) (2011 Oct) 165–175.

[30] Isaka M, Yasuda Y, Taniguchi T, Kozuka S, Matano K, Maeyama J, Morokuma K, Ohkuma K, Goto N, Tochikubo K. Mucosal and systemic antibody responses against an acellular pertussis vaccine in mice after intranasal co-administration with recombinant cholera toxin B subunit as an adjuvant. Vaccine 21 (11–12) (2003) 1165–1173.

[31] Asokanathan C, Corbel M, Xing D. A CpG-containing oligodeoxynucleotide adjuvant for acellular pertussis vaccine improves the protective response against Bordetella pertussis. Hum. Vaccines Immuno therapeutics 9 (2) (2014) 325–331.

[32] van Roosmalen ML, Kanninga R, El Khattabi M, Neef J, Audouy S, Bosma T, Kuipers A, Post E, Steen A, Kok J, Buist G, Kuipers OP, Robillard G, Leenhouts K. Mucosal vaccine delivery of antigens tightly bound to an adjuvant particle made from food-grade bacteria, Methods 38 (2) (2006) 144–149.

[33] Yeh CY, Yeh TH, Jung CJ, Chen PL, Lien HT, Chia JS. Activated imumannasal epithelial cells modulate specific antibody response against bacterial or viral antigens, PLoS One 8 (2) (2013) e55472.

[34] Van Braeckel-Budimir N, Haijema BJ, Leenhouts K. Bacterium-like particles for efficient immune stimulation of existing vaccines and new subunit vaccines in mucosal applications. Front. Immunol. 4 (2013) 282.

[35] Lu J, Hou H, Wang D, Leenhouts K, Roosmalen MLV, Sun T, Gu T, Song Y, Jiang C, Kong W, Wu Y. Systemic and mucosal immune responses elicited by intranasal immunization with a pneumococcal bacterium-like particle-based vaccine displaying pneumolysin mutant Plym2. Immunol. Lett. 187 (2017) 41–46.

[36] Ramirez K, Ditamo Y, Rodriguez L, Picking WL, van Roosmalen ML, Leenhouts K, Pasetti MF. Neonatal mucosal immunization with a non-living, non-genetically modified Lactococcus lactis vaccine carrier induces systemic and local Th1-type immunity and protects against lethal bacterial infection. Mucosal Immunol. 3 (2) (2010) 159–171.

[37] Ramasamy R, Yasawardena S, Zomer A, Venema G, Kok J, Leenhouts K. Immunogenicity of a malaria parasite antigen displayed by Lactococcus lactis in oral immunisations. Vaccine 24 (18) (2006) 3900–3908.

[38] Audouy SA, van Roosmalen ML, Neef J, Kanninga R, Post E, van Deemter M, Metselaar H, van Selm S, Robillard GT, Leenhouts KJ, Hermans PW. Lactococcus lactis GEM particles displaying pneumococcal antigens induce local and systemic immune responses following intranasal immunization. Vaccine 24 (26) (2006) 5434–5441.