Development of Recombinant Pertussis Vaccines

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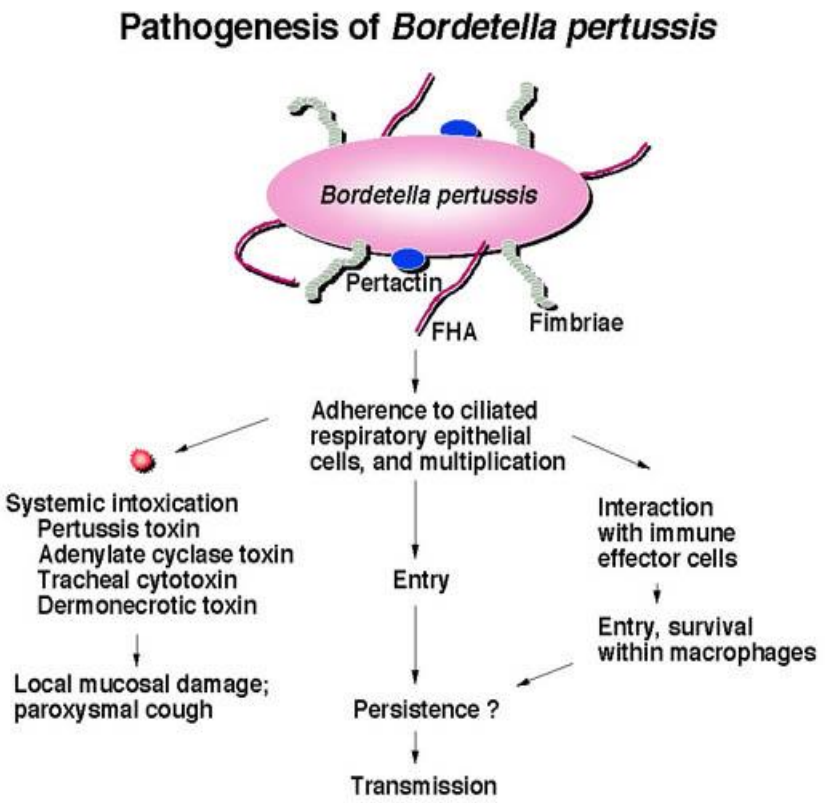
DCVMN Workshop: Global Registration and Vaccine Shortage

6-10 March 2017, Taipei, Taiwan

Bordetella pertussis

Pathogenesis



Source: http://www.my-pharm.ac.jp/~yishibas/research/Pertussis1.jpg

- **PT**
  - Principal toxin secreted by Bp, 5 subunits, A-B structure
  - Many pathologic effects mediated by ADP ribosylation of G protein effectors
- **FHA**
  - Filamentous adhesion factor
- **PRN ("69K")**
  - Impurity present in Japanese T-type vaccines
  - RGD sequences promoting adhesion to cells
- **Agg 2+3**
  - or Fimbriae

Pertussis Vaccines

Three Types of Vaccines

- **Whole-cell Pertussis vaccines (wP)**
- **Acellular Pertussis vaccines using chemically detoxified Pertussis Toxin (cPT)**
  - Co-purified antigens (Asia)
  - Individually purified antigens (Western countries)
- **Recombinant Pertussis vaccines**
  - Live-attenuated (nasal route)
  - Inactivated
    - Genetically-detoxified Pertussis Toxin (rPT)
    - Recombinant antigens such as PT, ACT, PRN…

Resurgence of Pertussis

An Increasing Concern Worldwide

- Waning immunity
- Genetic shifts of circulating Bp strains

Table 1. Possible Vaccination Strategies to Control the Resurgence of Pertussis

Strategy	Remarks
Return to the use of wcP	Probably unacceptable
Develop less-reactogenic wcP	Not yet done
Maternal vaccination to provide transplacental antibody to protect newborn	Now generally recommended
Vaccination of newborn contacts (cocoon strategy)	Difficult to obtain complete coverage
More frequent boosters with acP	Costly and difficult to put in place
Change antigens in acP to those from currently circulating strains	Uncertain effect
Increase quantities of current antigens	Would require large trials
Inactivate PT by genetic mutation or milder chemical	Probably advisable to increase immunogenicity
Add new virulence factors	Would require large trials
Use stronger adjuvants	May require large trials
Administer live attenuated *Bordetella pertussis* intranasally	Early development Probably best as a boost strategy

Abbreviations: acP, acellular pertussis vaccine; PT, pertussis toxin; wcP, whole-cell pertussis vaccine.

Sources:
1. WHO (2013)
2. Plotkin A. (2013) Clinical Infectious Diseases

Call for New Pertussis Vaccines

Genetically-Inactivated PT, the Solution ?

The Diphtheria and Pertussis Components of Diphtheria-Tetanus Toxoids–Pertussis Vaccine Should Be Genetically Inactivated Mutant Toxins

John B. Robbins,[1] Rachel Schneerson,[1] Birger Trollfors,[2] Hiroko Sato,[3] Yuji Sato,[3] Rino Rappuoli,[3] and Jerry M. Keith[1]

[1]National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland; [2]Department of Pediatrics, University of Göteborg, Sweden; [3]Chiron Vaccines, Siena, Italy

Vaccine

Vaccine 25 (2007) 2811–2816

The rise in pertussis cases urges replacement of chemically-inactivated with genetically-inactivated toxoid for DTP

John B. Robbins[a,*], Rachel Schneerson[a], Jerry M. Keith[a], Joseph Shiloach[b], Mark Miller[c], Birger Trollors[d]

Relative Contribution of Th1 and Th17 Cells in Adaptive Immunity to *Bordetella pertussis*: Towards the Rational Design of an Improved Acellular Pertussis Vaccine

Pádraig J. Ross[1], Caroline E. Sutton[1,3], Sarah Higgins[1,3], Aideen C. Allen[1], Kevin Walsh[1], Alicja Misiak[1], Ed C. Lavelle[2], Rachel M. McLoughlin[3], Kingston H. G. Mills[1]*

1 Immune Regulation Research Group, School of Biochemistry and Immunology, Trinity Biomedical Sciences Institute, Trinity College Dublin, Dublin, Ireland, **2** Adjuvant Research Group, School of Biochemistry and Immunology, Trinity Biomedical Sciences Institute, Trinity College Dublin, Dublin, Ireland, **3** Host Pathogen Interactions Group, School of Biochemistry and Immunology, Trinity Biomedical Sciences Institute, Trinity College Dublin, Dublin, Ireland

Genetically Detoxified Pertussis Toxin Induces Th1/Th17 Immune Response through MAPKs and IL-10-Dependent Mechanisms[1]

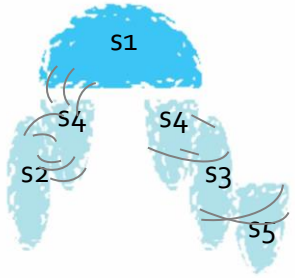
Maria Nasso,[2]* Giorgio Fedele,[2]* Fabiana Spensieri,[3]* Raffaella Palazzo,* Paolo Costantino,[†] Rino Rappuoli,[†] and Clara Maria Ausiello[4]*

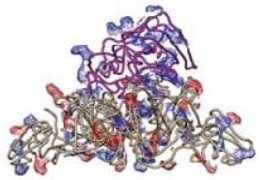
Genetically Detoxified Pertussis Toxin

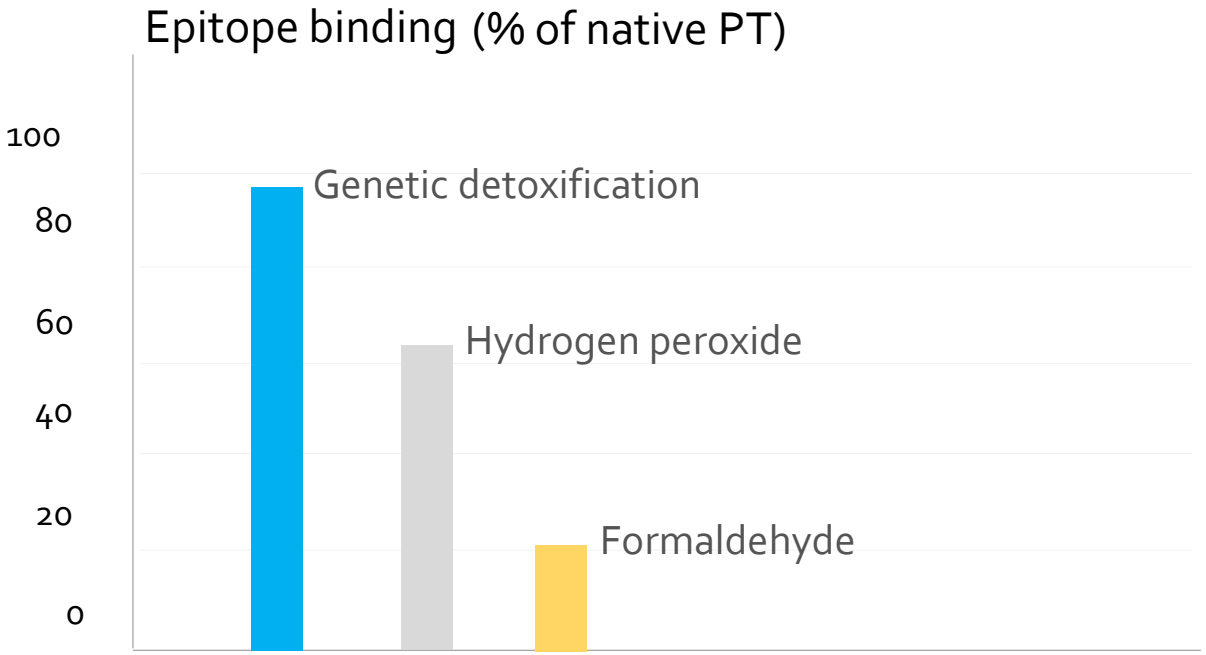
A Non-Toxic and Superior Immunogen

rPT is a PT devoid of toxicity while maintaining the other properties of the native PT.

cPT introduces dramatic changes on the toxin surface.







- Chemical treatment can destroy up to 80% of surface epitopes
- The rPT preserves the epitopes for T-cell binding significantly better than cPT.

Source: Ibsen H (1996)

WHO Position Pater on Pertussis Vaccines

Recommendations

Pertussis (whooping cough) is an important cause of death in infants worldwide, and continues to be a public health concern despite high vaccination coverage. In 2013, according to WHO estimates, pertussis was still causing around 63 000 deaths in children aged <5 years. Two types of pertussis vaccines are available: wP vaccines and aP vaccines.

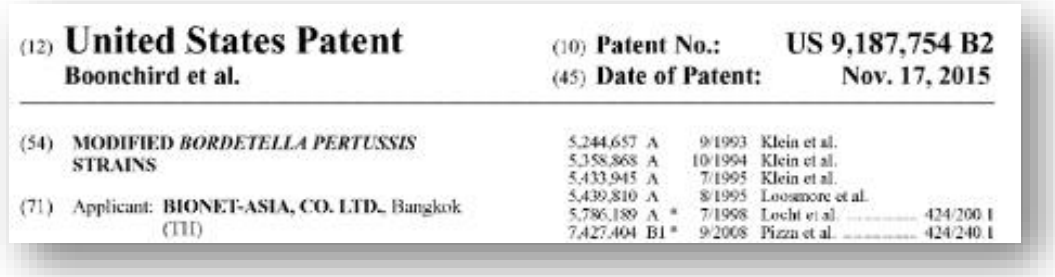
A switch from wP to aP vaccines for the primary schedule should only be considered if additional periodic booster or maternal immunization can be assured and sustained. National programmes currently administering wP vaccination should continue to use wP vaccines for primary vaccination series. National programmes currently using aP vaccine may continue using this vaccine but should consider the need for additional booster doses and additional strategies such as maternal immunization in case of resurgence of pertussis.

BioNet Patented Pertussis Technology

Translational Research: From Concept to Clinical Proof

Mahidol University Research Team

from left: Mr. Wasin Buasri, Assoc. Prof. Dr. Chuenchit Boonchird, Prof.Dr. Watanalai Panbangred, Dr. Attawut Impoolsup, Dr. Pramvadee Wongsaengchantra, Ms. Anocha Nuchtas, Ms. Kanyapak Sapsanyakorn



(12) **United States Patent**
Boonchird et al.

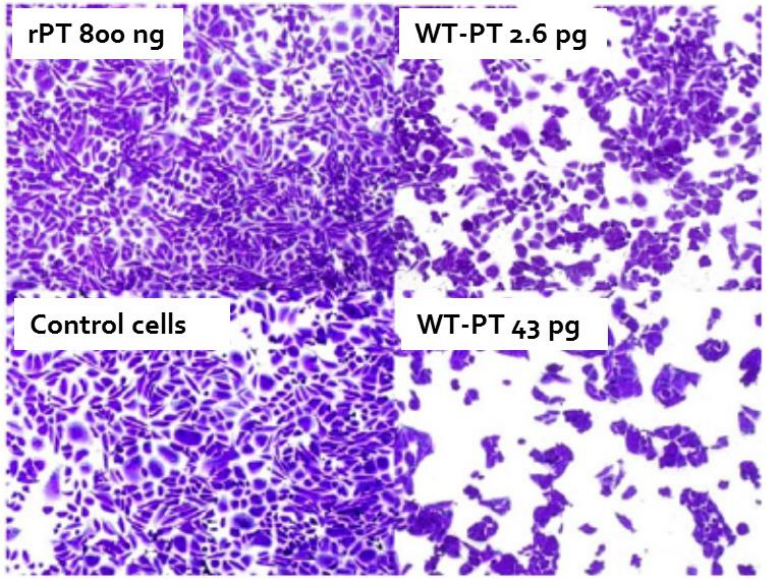
(10) **Patent No.: US 9,187,754 B2**
(45) **Date of Patent: Nov. 17, 2015**

(54) **MODIFIED *BORDETELLA PERTUSSIS* STRAINS**

(71) Applicant: **BIONET-ASIA, CO. LTD.**, Bangkok (TH)

5,244,657	A	9/1993	Klein et al.	
5,358,868	A	10/1994	Klein et al.	
5,433,945	A	7/1995	Klein et al.	
5,439,810	A	8/1995	Loosmore et al.	
5,786,189	A *	7/1998	Locht et al.	424/200.1
7,427,404	B1 *	9/2008	Pizza et al.	424/240.1

- **BioNet Genetically detoxified PT (PTgen)**
  - Mutation in two positions
    - Two amino-acids replaced
    - ARG9 to LYS9 and GLU129 to GLY129
  - Resulting in the loss of catalytic and toxic effects



Source: Buasri *et al.* (2012) *BMC Microbiology* 12:61

Clinical Phase I/II Study

Procedure Overview

- Randomized, Observer-blind and controlled study (TCTR20140703001)
- **Objective:** To assess safety and immunogenicity of a single injection of BNA's aP or BNA's TdaP or licensed TdaP (Adacel®; Sanofi Pasteur) vaccines
- **Study Population:** Healthy adult volunteers (Male & Female), 18-35 years of age
- **Number of Subjects:** 60 (20 per group)
  - Group 1 – BNA's aP
  - Group 2 – BNA's TdaP
  - Group 3 – Licensed TdaP (Adacel®, Sanofi Pasteur) as comparator
- **Study site:** Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

Source: Sirivichayakul C *et al.* (2017) *Human Vaccin Immunother*

Study Vaccines

Vaccine Composition

- Presented in pre-filled syringe for intramuscular injection

Active ingredients per 0.5-mL dose	BNA's aP	BNA's TdaP	Adacel®
Tetanus toxoid (TT)	-	7.5 Lf	5 Lf
Diphtheria toxoid (DT)	-	2.0 Lf	2 Lf
Pertussis toxoid (PT)	5 µg*	5 µg*	2.5 µg
Filamentous hemaglutinin (FHA)	5 µg	5 µg	5 µg
Pertactin (PRN)	2.5 µg	2.5 µg	3 µg
Fimbriae type 2/3	-		5 µg

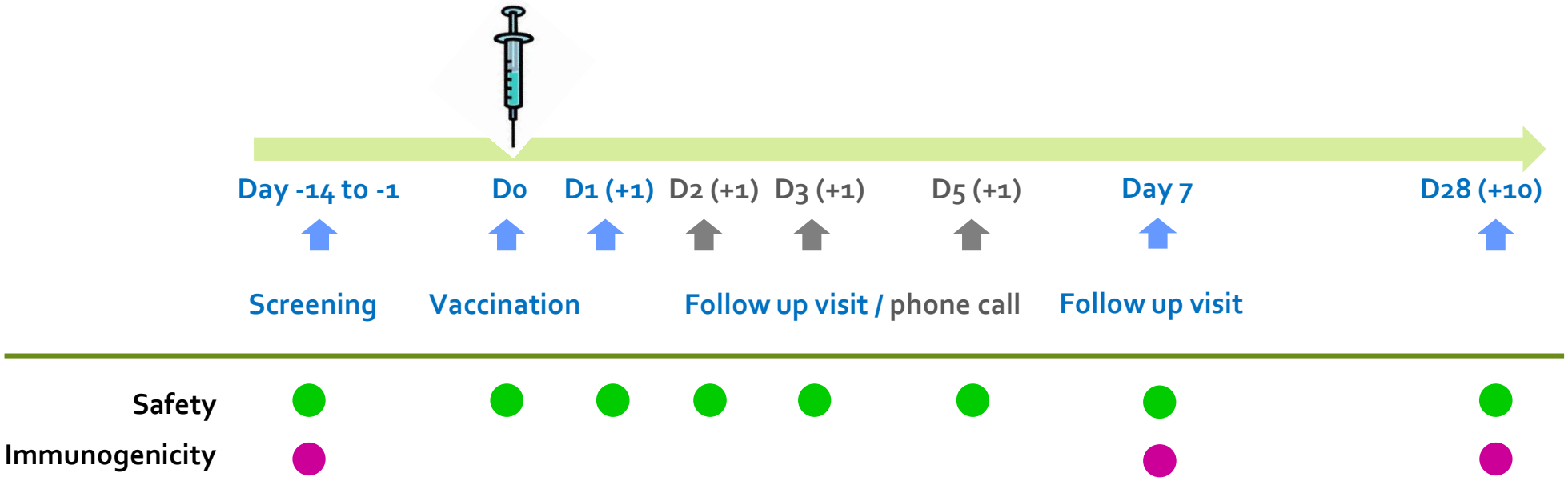
* Recombinant Pertussis Toxin (PTgen)

Lf = Limit of flocculation

Source: Sirivichayakul C *et al.* (2017) *Human Vaccin Immunother*

Study Procedure

Single Injection with 28 Days Follow-up



- The study was conducted according to ICH-GCP guidelines.
- EC approval of the study and individual consent were obtained.
- Safety and Immunogenicity assessment were conducted according to GLP or relevant guidelines using standardized methods.

Source: Sirivichayakul C *et al.* (2017) *Human Vaccin Immunother*

Safety

Solicited Local & Systemic Reactions at Day 7

	n (%)			
	BNA's aP (*n* = 20)	**BNA's TdaP (*n*=20)**	**Adacel® (*n*=20)**	***P*-value***
LOCAL REACTIONS				
Pain	16 (80.00)	15 (75.00)	17 (85.00)	0.73
Redness	0 (0.00)	3 (15.00)	1 (5.00)	0.15
Induration	0 (0.00)	4 (20.00)	1 (5.00)	0.06
SYSTEMIC REACTIONS				
Fever	0 (0.00)	0 (0.00)	1 (5.00)	-
Headache	2 (10.00)	1 (5.00)	3 (15.00)	0.86
Fatigue	3 (15.00)	2 (10.00)	5 (25.00)	0.43
Arthralgia	1 (5.00)	2 (10.00)	3 (15.00)	0.86
Chills	1 (5.00)	0 (0.00)	1 (5.00)	-
Malaise	1 (5.00)	1 (5.00)	5 (25.00)	0.08
Myalgia	5 (25.00)	2 (10.00)	7 (35.00)	0.21
Vomiting	0 (0.00)	0 (0.00)	0 (0.00)	-

*; Fisher's exact and P < 0.05 considering as statistically significant

Source: Sirivichayakul C *et al.* (2017) *Human Vaccin Immunother*

Safety

Solicited Adverse Events during 28 days Post-vaccination

Summary	*n* (%)			
	BNA's aP (*n* = 20)	**BNA's TdaP (*n*=20)**	**Adacel® (*n*=20)**	**Total**
Adverse events				
with one or more AEs	5 (25.00)	5 (25.00)	4 (20.00)	14 (23.33)
vaccine-related AEs	1 (5.00) [a]	1 (5.00) [b]	1 (5.00) [b]	3 (5.00)
with no AE	15 (75.00)	15 (75.00)	16 (80.00)	46 (76.67)
discontinued due to an AE	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Serious adverse events				
with SAE	1 (5.00) [c]	0 (0.00)	0 (0.00)	1 (1.67)
vaccine-related SAE	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
discontinued due to a SAE	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

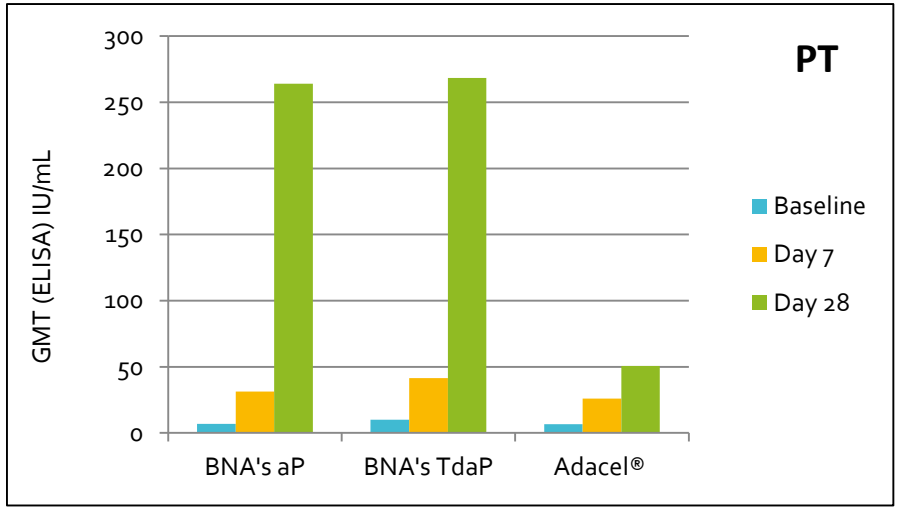
[a] Arm pain [b] Vaccination site pain

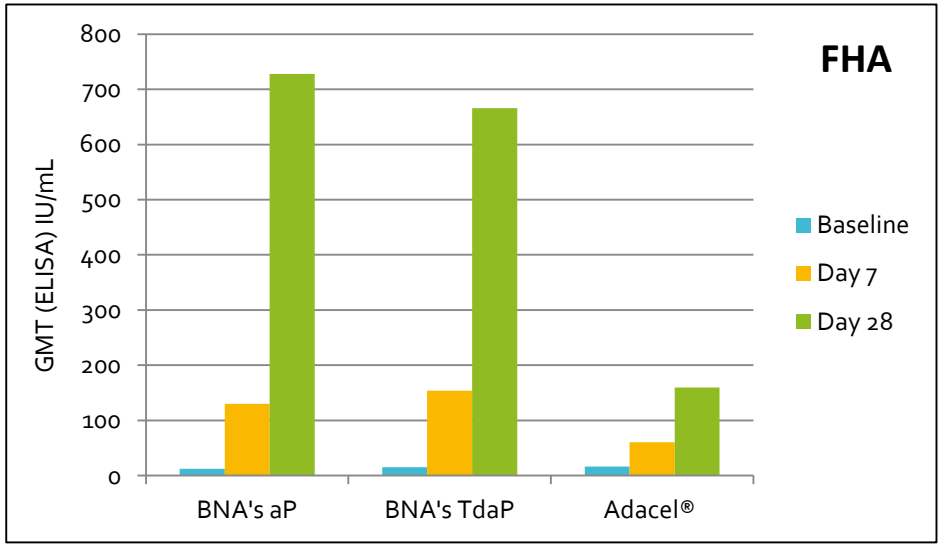
Source: Sirivichayakul C *et al.* (2017) *Human Vaccin Immunother*

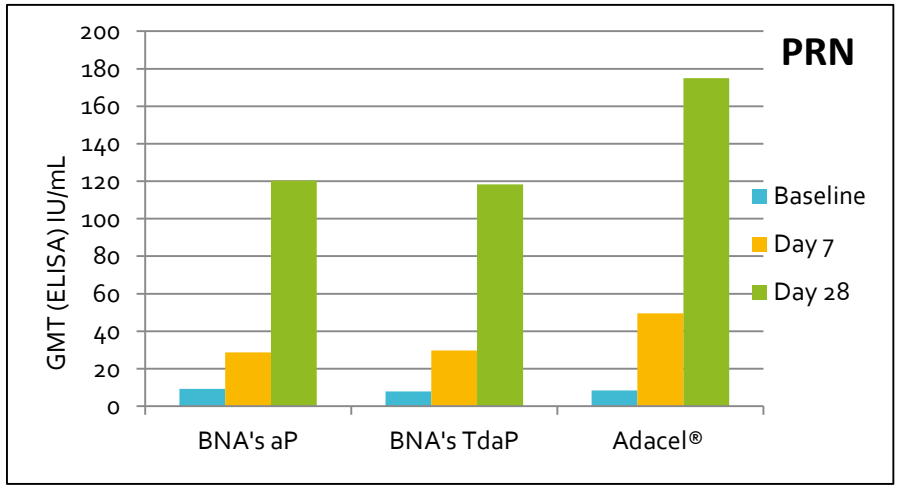
Immunogenicity

ELISA Total IgG Anti-pertussis GMT at Day 28 (Post-vaccination)

Seroconversion rate	Day 28			
	BNA's aP 19 n (%) (95% CI)	BNA's TdaP 18 n (%) (95% CI)	Adacel® 19 n (%) (95% CI)	P-value
Anti-PT ELISA	17 (89.47) (76.0–100.0)	17 (94.44) (84.0–100.0)	16 (84.21) (68.0–100.0)	0.862 [2]
Anti- FHA ELISA	19 (100.00) (100.0–100.0)	17 (94.44) (84.0–100.0)	16 (84.21) (68.0–100.0)	0.209 [2]
Anti-PRN ELISA	15 (78.95) (61.0–97.0)	15 (83.33) (66.0–100.0)	16 (84.21) (68.0–100.0)	1.000 [2]
Anti-PT Nab	17 (89.47) (76.0–100.0)	16 (88.89) (74.0–100.0)	16 (84.21) (68.0–100.0)	1.000 [1]



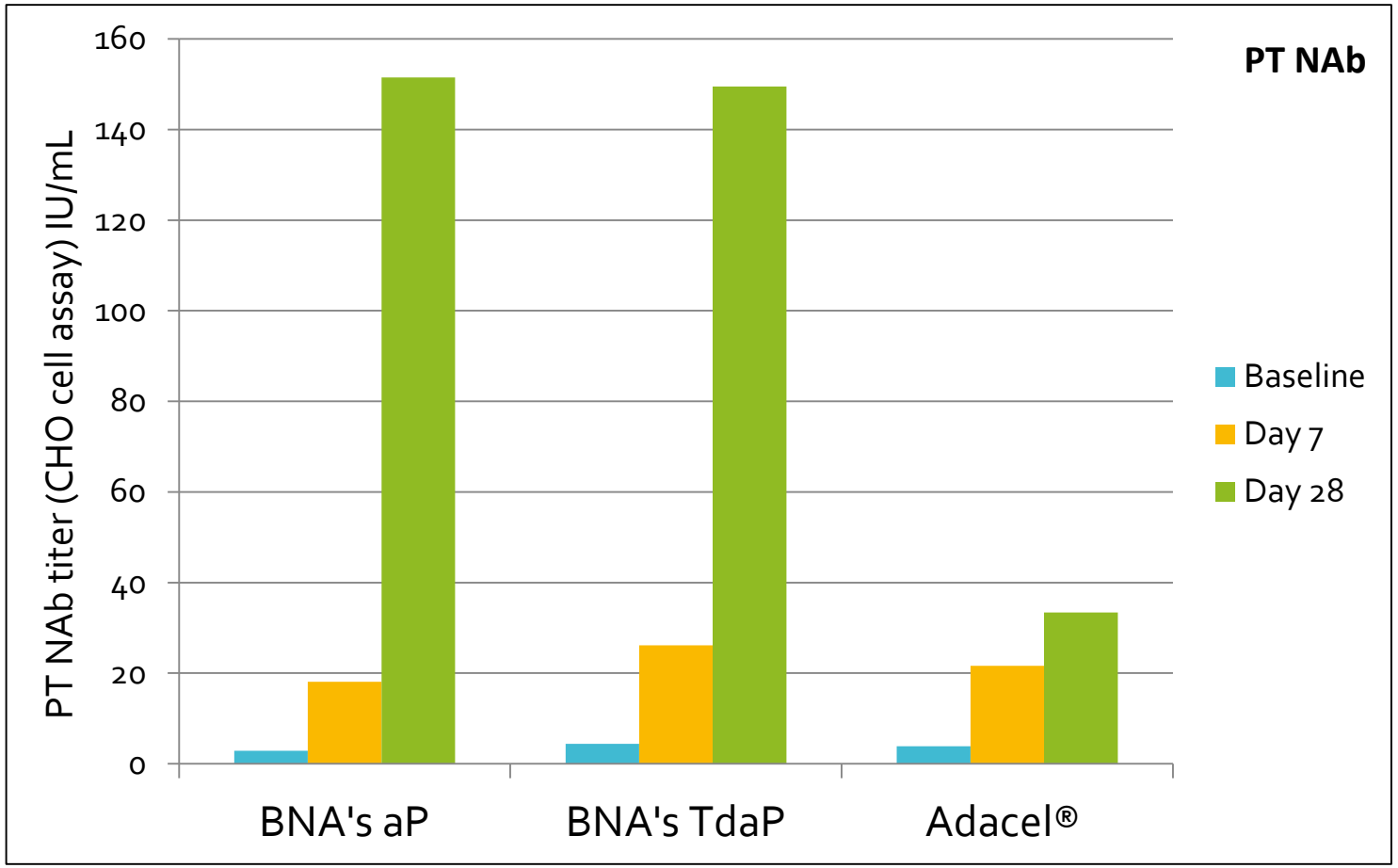




Source: Sirivichayakul C *et al.* (2017) *Human Vaccin Immunother*

Immunogenicity

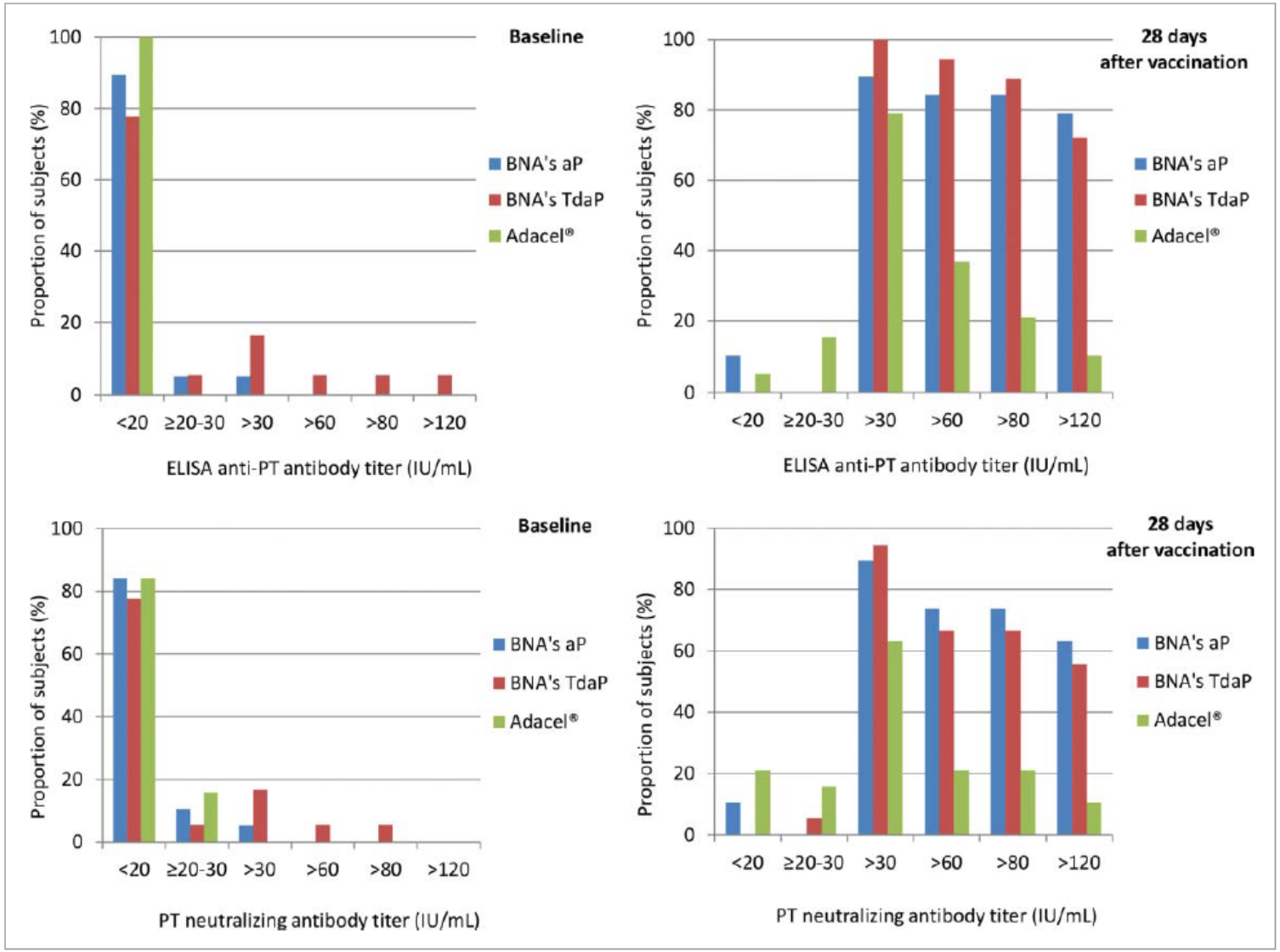
Anti-PT Neutralizing Titers at Day 28 (Post-vaccination)



Source: Sirivichayakul C *et al.* (2017) *Human Vaccin Immunother*

Immunogenicity

Proportion of Subjects at Various Cut-off Titers



Source: Sirivichayakul C *et al.* (2017) *Human Vaccin Immunother*

DCVMN Workshop Taiwan 2017

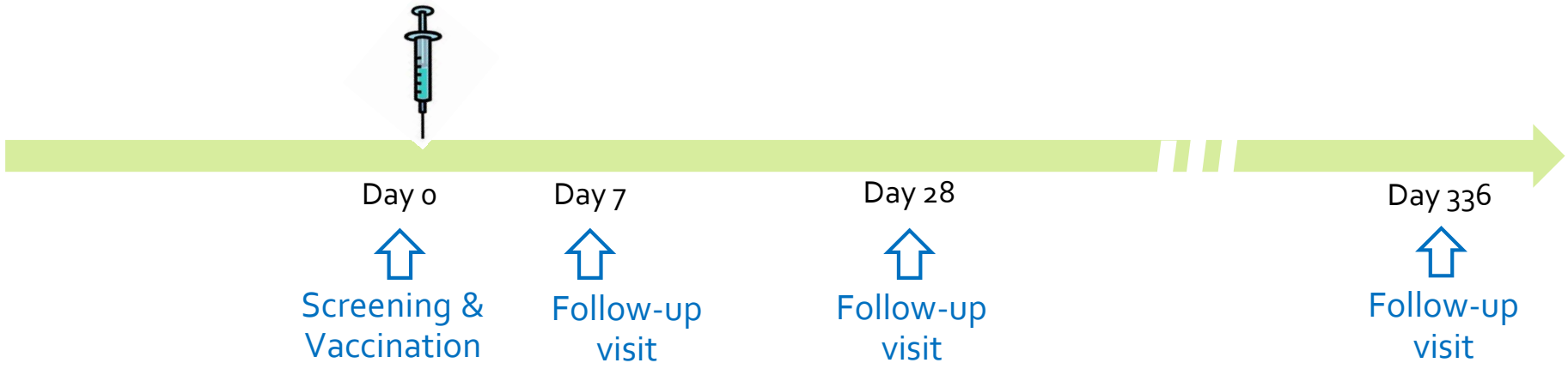
Clinical Phase II/III Study

A Pivotal Study in Thailand in 12-17 Years of Age

- **Objectives:**
  - **Primary:** To demonstrate non-inferior immunogenicity of one dose of BioNet's combined Tetanus, reduced dose of Diphtheria and acellular Pertussis vaccine (Boostagen™) as compared to Adacel® vaccine.
  - **Secondary:**
    - To assess safety of Boostagen™ and Pertagen™ vaccines and to demonstrate non-inferior immunogenicity of Pertagen™ vaccine as compared to Adacel®.
    - To assess immunopersistence at 1 year.
- **Primary endpoint:**
  - Non-inferior immunogenicity – antibody response in all subjects
  - Seroconversion rates as defined by proportion of subjects with ≥ 4-fold increase with respect to baseline of ELISA antibodies to PT and FHA in Boostagen™ and Adacel® vaccine groups.

Study Design

Single Injection with 28 Days and 1 Year Follow-up



	Day 0	Day 7	Day 28	Day 336
Safety	●	●	●	●
Immunogenicity				
GMT Ab (ELISA)	●		●	●
PT NAb (CHO)	●		●	●
CMI	●		●	●

● A subset of 50 subjects/group

● A subset of 20 subjects/group

BioNet Clinical Study

Summary

Results

Local and systemic post-immunization reactions at seven days after vaccination and incidence of Adverse Events one month after vaccination were similar in the three vaccine groups. One unrelated Serious Adverse Event was reportedin one subject in the Pertagen® group. ELISA anti-PT, ELISA anti-FHA, and anti-PT neutralizing antibody GMTs as well as serconversion rate (≥ 4 fold increase) were statistically significant higher in Pertagen® and Boostagen® vaccine groups than in Adacel® group ($p \leq 0.05$). Non-inferiority of Pertagen® and Boostagen® vaccines *vs* Adacel® vaccine was demonstrated (difference level 10%).

Conclusions

The newly developed aP vaccines either standing alone (Pertagen®) or in formulation as TdaP (Boostagen®) showed to be as tolerated and safe as Adacel®. The higher ELISA and neutralizing anti-PT titres observed in Pertagen® and Boostagen® vaccine groups vs Adacel® vaccine group are consistent with epitopes conservation of the genetically detoxified PT.

BioNet PTgen delivered via Innovative Patch

Initiating Phase I Study in Europe in 2016 after Pre-Clinical Proof of Concept

dbv technologies

HUG Hôpitaux Universitaires Genève

BioNet

DBV Technologies, BioNet-Asia and Geneva University Hospitals Complete Dosing in First Cohort of Phase I Study of Viaskin rPT for Booster Vaccination Against Pertussis

DSMB expressed no safety concerns with Viaskin rPT 25 µg

Following positive DSMB review, dosing with Viaskin rPT 50 µg has been initiated

PARIS, BANGKOK and GENEVA November 17, 2016 - DBV Technologies (Euronext: DBV – ISIN: FR0010417345 - Nasdaq Stock Market: DBVT), the Geneva University Hospitals (HUG) and BioNet-Asia Co. Ltd today announced

BioNet Pertagen Vaccine Evaluated in Europe

Phase II Study in Adolescents

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

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Text Size

The PertADO Geneva Trial

This study is currently recruiting participants. (see Contacts and Locations)

Verified October 2016 by University Hospital, Geneva

Sponsor:
Siegrist Claire-Anne

Collaborator:
BioNet-Asia Co., Ltd.

Information provided by (Responsible Party):
Siegrist Claire-Anne, University Hospital, Geneva

ClinicalTrials.gov Identifier:
NCT02946190

First received: October 24, 2016
Last updated: October 28, 2016
Last verified: October 2016
History of Changes

Thank you

"A world free of any preventable disease is our dream. To make this dream come true
is our mission."