Foundation Merieux #2

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Less Reactogenic DTwP

Mattel Children's Hospital at UCLA

The Need for New Less Reactogenic Whole Cell Vaccines

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Perspectives-2015

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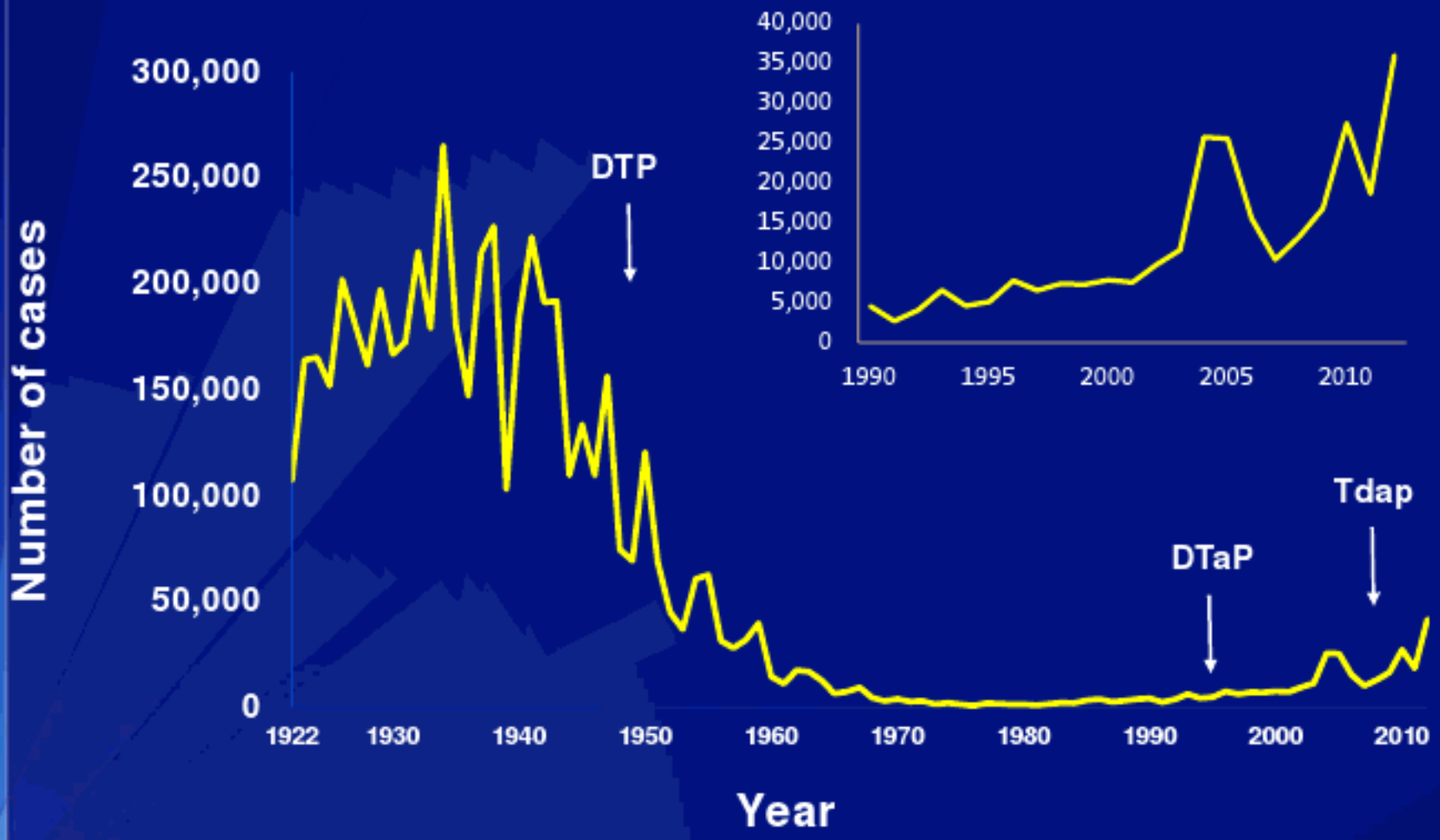
Reported NNDSS pertussis cases: 1922-2012*



*2011 data are provisional; 2012 data are provisional.

SOURCE: CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System and 1922-1949, passive reports to the Public Health Service

Pertussis Fact # 1

"The rate of reported pertussis today is ~20 fold less than in the prevaccine era."

Pertussis Fact # 2

"Illness in DTaP vaccine failures is less severe than illness in similar aged unvaccinated children."

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Possible Reasons for the "Resurgence" of Reported Pertussis

1) Genetic changes in *B. pertussis*
2) Lessened potency of pertussis vaccines
3) Waning of vaccine-induced immunity
4) Greater awareness of pertussis
5) The general availability of better laboratory tests

Possibility of New Pertussis Vaccines

- DTaP- “many problems”.
- Live vaccine – “priming by DTwP is better than priming by infection”.
- DTwP with modified LPS – “will need to be no more reactogenic than DT”.

New DTaP Vaccines

Possible Reasons Why Acellular Pertussis Vaccines Fail

- A Th 1/Th 2 vs a Th 17 and Th 1 response in DTaP vaccinees
- Incomplete antigen package.
- Incorrect balance of antigens in the vaccine.
- Linked-epitope suppression.
- ELISA values measured are cross reacting antibodies.
- Genetic changes in *B. pertussis*

The Type of T Cell Immune Response*

- "Previously infected animals and wP-vaccinated animals possess strong *B. pertussis*- specific T helper 17 (Th17) memory and Th1 memory, whereas aP vaccination had a Th1/Th2 response instead". (Warfel et. al. PNAS. 2014; 111:787-92).
- The Th17/Th1 response prevents infection as well as disease.
- This Th17/Th1 response gives longer protection than a Th1/Th2 response.

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Incomplete Antigen Package

Vaccine Efficacies of Eight Acellular Pertussis Component Vaccines*

Vaccine	Components	Percent Efficacy (95% CI)
Amvax	PT	31(-4-59)
JNIH-7	PT	-6(-49-24)
JNIH-6	PT, FHA	43(15-61)
SKB	PT, FHA	42(33-51)
SKB	PT, FHA, PRN	71(60-78)
Chiron-Biocine	PT, FHA, PRN	71(61-79)
Lederle/Takeda	PT, FHA, PRN, FIM-2	62(38-77)
Connaught (Canada)	PT, FHA, PRN FIM-2,3	78(73-82)

* >6 days of cough

Incorrect Balance of Antigens in the Vaccine

- Cherry J.D. et al. Vaccine. 1998;16: 1901-1906
- Storsaeter J.et al. Vaccine. 1998; 16: 1907-1916

Logistic Regression Coefficients on the Relationship Between High and Low Antibody Values* in 87 Subjects who were Cases or Noncases Following Household Exposure. A Negative Coefficient Indicates a Decrease in Disease Risk (Protection) and a Positive Coefficient Indicates an Increase in Disease

	Constant	Specific Antibody			
		PRN	FIM-2	PT	FIM-2+PT
Coefficient	0.70	-1.30	-1.33	-0.09	+0.89
SE‡	+/-0.41	+/-0.59	+/-0.90	+/-0.88	+/-1.24
P values	-	0.03	0.14	0.92	0.47

***High/low cut points are: PT 5.7 EU/ml; FHA 7 EU/ml; pertactin 8 EU/ml; and fimbriae-2 1.5 EU/ml**

‡Coefficient standard error

Logistic Regression Coefficients on the Relationship Between High and Low Antibody Values in 209 Subjects who were Cases or Non cases Following Household Exposure. A Negative Coefficient Indicates a Decrease in Disease Risk (Projection) and a Positive Coefficient Indicates an Increase in Diseases†

	Constant	Serum Antibody			
		PRN	FIM	PT	FIM+PT
Coefficient	2.003	-1.990	-1.548	-0.146	+1.148
p values	-	<0.05	<0.05	>0.05	>0.05

***High= ≥5EU/ml; Low= <5 EU/ml**

† Storsaeter et al Vaccine 1998;16:1907-16

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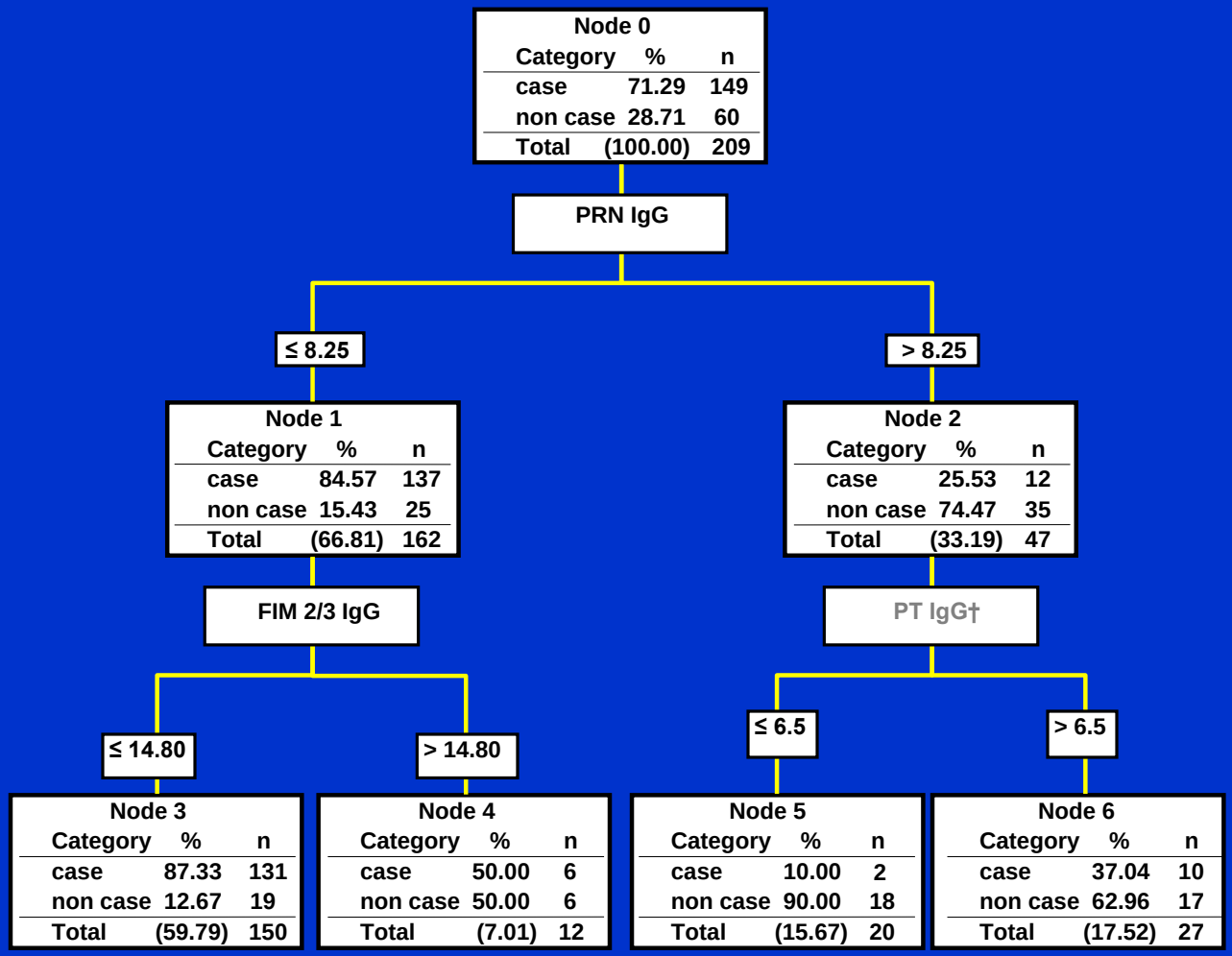
Classification Tree Analysis in 209 Household Exposed Children in Swedish Efficacy Trial *



* All GMTs expressed as EU/ml

† For pertactin > 8.25, this tree uses PT instead of FIM. chisq=4.417, p = 0.0467

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What is the Explanation for the Antagonism between PT and FIM and also between PT and PRN?

- Weiss et al (Infection and Immunity, 2004;72:7346-7951) examined complement killing of *B. pertussis* in the sera of APERT vaccinees. They noted a complement- blocking activity in some post-immunization sera.

- It seems likely that high levels of antibody to PT have a blocking activity on the agglutination of the organism by antibody to FIM or on PRN which decrease complement mediated bactericidal activity.

Geometric Mean Antibody Values (Eu/ml) at Seven months of Age in Children Immunized at 2, 4 and 6 months of age

Antigen	Vaccine			
	DTP (80)	DTaP2 (67)	DTaP 3 (80)	DTaP 5 (80)
PT	10	61	150	52
FHA	34	105	19	57
PRN	150	< 1	123	134
FIM	677	< 1	< 1	352

From Technical Report Trial 2 Swedish Institute for Infectious Disease Control, 1997

Linked-Epitope Suppression*

* Cherry J.D. et al.Clinical and Vaccine Immunology. 2010; 17: 741-747

Linked-Epitope Suppression

- The finding of initial priming by DTwP leading to greater efficacy than priming by DTaP can be explained by linked-epitope suppression caused by preferential responses of memory B cells following secondary exposure to vaccine components.
- Memory B cells out compete naïve B cells for access to the *Bordetella* epitopes as they are more numerous and their receptors exhibit a higher antigen affinity.
- Linked-epitope suppression applies as the immune response to novel epitopes is suppressed by the strong response to initial components if they are introduced together.

Pertussis Reports (Queensland, Australia) Between 1999 and 2011 for children Born in 1998 (N=40,691)*

		Incidence (95% CI)		
	No. of Reports	Average Annual Rate	Rate Difference	Rate Ratio
Preepidemic (1999-2008)				
Pure course				
DTaP primary course (n =9827)	13	13.2 (7.0 to 22.6)	8.0 (0 to 15.8)	2.53 (1.06 to 6.07)
DTwP primary course (n=22,956)	12	5.2 (2.7 to 9.1)	1 [Reference]	1 [Reference]

* Sarah L. Sheridan et al. JAMA 2012; 308, 454-456

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Comment Relating to Linked-Epitope Suppression

- DTwP vaccines may contain ~3000 proteins. Antibody to many of these proteins contribute to protection.
- DTaP vaccines contain up to 5 proteins.

ELISA Values Measured are Cross Reacting Antibodies

Predicted Duration of GMTs of IgG Antibodies to *B pertussis* Antigens following Adolescent and Adult Immunization* (Le et al JID 2004;190:535-44)

Antibody	Duration in Years ±SE above the LOQ
PT IgG	2.3 ±0.9
FHA IgG	7.6 ±4.4
PRN IgG	9.1 ±9.3

*GSK vaccine

† PT LOQ= 6 EU/ml; FHA and PRN LOQ= 8EU/ml.

Genetic Changes in *B. pertussis*

Genetic Changes in *B. pertussis* Proteins

- *Ptx* P1 allele to *ptx* P3 allele.
- PRN deficient mutants.
- Increase in *fim* 3B strains in U.S.

Genetic Changes in *B. pertussis*- 2015

- Vaccine pressure has resulted in changes in PT,PRN and FIM. Of these only PRN deficient mutants are presently important.
- Since DTwP vaccines contain multiple antigens PRN deficient mutants will not contribute to vaccine failure.
- Since DTaP and Tdap vaccines contain fewer antigens it seems clear that PRN deficient mutants will contribute to vaccine failure.

“Difficult to prove PRN deficient mutants contribute to vaccine failures because antibody to the B subunit of PT provides considerable efficacy against typical pertussis”

Live Pertussis Vaccines

Misconception #1

"Immunity following pertussis is lifelong whereas immunity following immunization (either DTwP or DTaP) is relatively short lived."

Evidence Against Lifelong Immunity following *B. pertussis* Infection

1). Historical

2). My experience in Germany and the U.S.

3). Comparison of IgA and IgG antibodies to *B. pertussis* antigens in sera of young German and American adults

Comparison of Geometric Mean IgG Anitbody Values* and Agglutinin Titersº in American and German Young Adults

(Cherry et al CID 1995; 20: 1271-74)

Antigen	American Students n=119	German Military n=119	P-value
Agglutinogens +	104.1	50.5	<0.0001
Fimbriae-2	52.0	11.7	<0.0001
FHA	56.4	31.4	0.001
PT	16.9	5.4	0.0001
Pertactin	33.3	15.6	0.0002

* Expressed as ELISA units/mL.

º Expressed as reciprocal of serum dilution.

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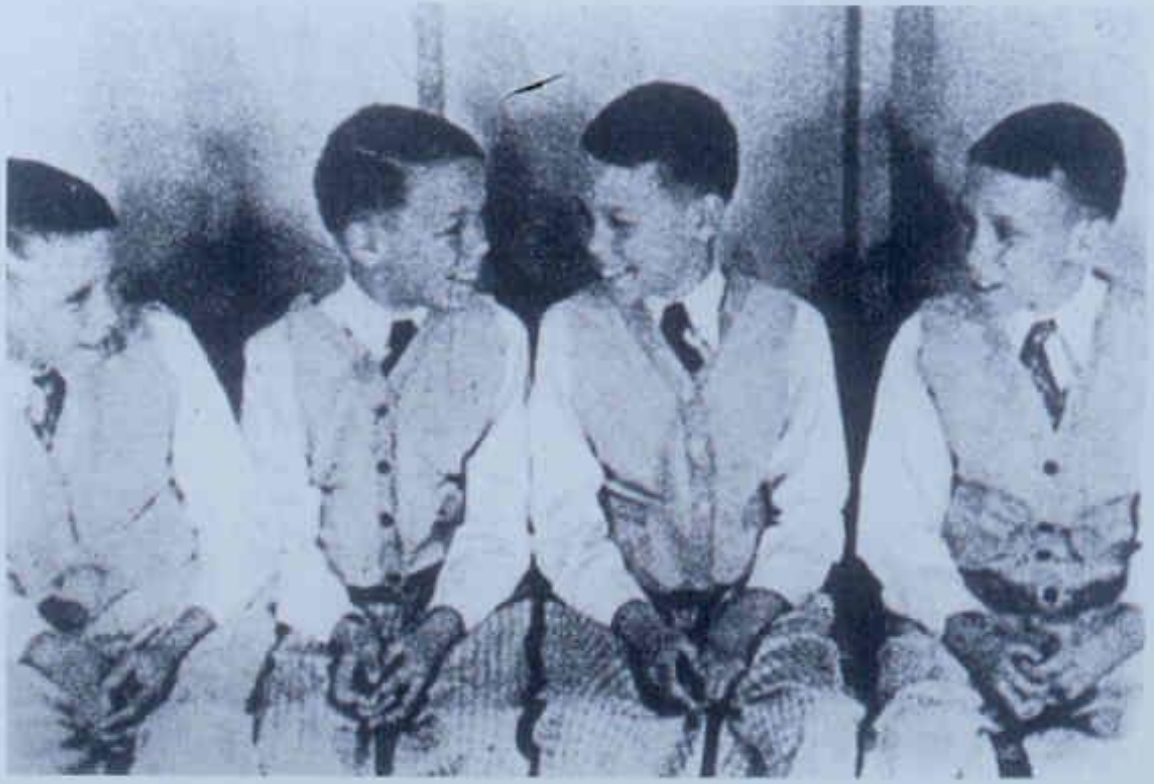
Comparison of Geometric Mean IgA Antibody Values* in American and German Young Adults

(Cherry et al CID 1995; 20: 1271-74)

Antigen	American Students n=119	German Military n=119	P-value
Fimbriae-2	8.3	6.7	0.35
FHA	11.9	14.2	0.42
PT	3.8	3.1	0.39
Pertactin	8.1	10.1	0.21

* Expressed as ELISA units/mL.

DTwP Vaccines



Source. National Library of Medicine.

FIGURE 2—The 4 sons of an Illinois physician featured in Louis Sauer's 1933 pertussis vaccine experiment.

AM J. Pub Health 2000; 90: 199-207

DTwP Vaccine Reactions

Less Serious Reactions Following 15,752 DTP and 784 DT Immunizations

Reaction	DTP Group		DT Group		*P* Value
	No.	(%)	No.	(%)	
Local reactions					
Redness	5,891	37.4	60	7.6	<.0001
Swelling	6,411	40.7	60	7.6	<.0001
Pain	8,018	50.9	78	9.9	<.0001
Systemic reactions					
Fever (≥ 38 C)*	3,605	46.5	27	9.3	<.0001
Drowsiness	4,962	31.5	117	14.9	<.0001
Fretfulness	8,412	53.4	177	22.6	<.0001
Vomiting	977	6.2	20	2.6	<.0001
Anorexia	3,292	20.9	55	7.0	<.0001
Persistent crying	488	3.1	5	0.7	.0003
High-pitched, unusual cry	17	0.1	0	0.0	.3574

*Fever was evaluated following 7,753 DTP and 292 DT immunizations. Children whose temperature was recorded at three and six hours after immunization are reported.

From Cody et al. Pediatrics. 1981;68:650-660

More Serious Reactions in 15,752 DTwP Vaccinees*

- 9 Hyponic hyporesponsive episodes
- 9 Seizures

* Cody et al.Pediatrics.1981;68:650-60

DTwP Reactions and Endotoxin Content in 20 Vaccine Lots*

- Fever increased in frequency from 20.6% in children immunized with vaccine lots that contained 2,500 EU to 55.1% in children immunized with lots containing 40,000 EU.
- Drowsiness and anorexia decreased in frequency with increasing endotoxin content.

* Baraff et al.PIDJ;8:502-7

Developing a New Less Reactogenic DTwP Vaccine

Bordetella pertussis
Lipooligosaccharide

Unique Aspects of *B.pertussis* LOS

- LOS is the major cause of DTwP vaccine reactions
- LOS causes no symptoms in pertussis
- The mouse model in not satisfactory for the study of *B.pertussis* LOS

Attempts to Remove or Modify Endotoxin in Pertussis Vaccines

- Incubation of DTwP vaccine with Polymyxin B (Cooperstock and Riegle. Infection and Immunity.1981;33:315-8)
- Percolation through a polymyxin-Sepharose,affinity chromatography column (Bannatyne et al. Vaccine.1986;4:91-2

Attempts to Remove of Modify Endotoxin in Pertussis Vaccines (Continued)

- Instituto Butantan in San Paulo,Brazil has produced (by chemical extraction of LOS from the outer membrane)and tested in children a DTwP vaccine (“Plow”) .
- However their published papers seem to be more PR than factual. (Dias et. al.Human Vaccines & Immunotherapeutics.2012;9:339-48; Zorzeto et al.Clinical and Vaccine Immunology.2009;16:544-50)

Facts Relating to LOS

- *B.pertussis* infection or DTwP imminization in children results in the development of antibody to LOS.
- LOS is an agglutinogen. Therefore antibody to LOS will be an anti-adhesin.
- LOS is potent adjuvant.
- Antibody to LOS has complement-dependent bactericidal activity.

What Characteristics Will a New DTwP Vaccine Need?

- A reactogenicity profile not significantly greater than present DTaP vaccines.
- An immune response similar to a good DTwP vaccine such as the Evans vaccine.
- In should contain modified LOS.

Our View (Rachel Fernandez and Me) on How to Make a New Less Reactogenic DTwP Vaccine

“Fix only that which is broken-endotoxin”

In the Efficacy Trials of the 1990s there were 4 DTwP Vaccines that had greater Efficacy than the DTaP Vaccines Being Evaluated

- Pasteur Merieux
- Behringwerke A.G.
- Lederle
- Evans

Our Approach

- Modify the endotoxin of an “available” DTwP vaccine.
- Compare the immune response of the modified vaccine with the original vaccine in mice.
- Do reactogenicity studies in TC, animals and then people.
- Would hope that efficacy could be established by bridging.
- Reactogenicity would be evaluated in field studies.

Summary

- New vaccines (DTaP, DTwP, and live vaccine) are all possible but will require ~5-10 years before use.
- Immunity after DTwP is better than after infection.
- My bridging proposal for a new DTwP vaccine might take only ~2-3 years.
- We don't know if it is possible to make an effective DTwP vaccine with an acceptable reactogenicity profile.

Questions/Comments